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DEVELOPMENT OF A SOLID DOSAGE FORM WITH ADSORPTION ACTIVITY

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Enterosorbents are produced in various dosage forms – powders, tablets, pastes, etc., some of them are also manufactured in the form of capsules. A water-soluble polysaccharide complex (WSPC) manifesting a pronounced adsorption activity, which determines the prospects for the development of dosage forms of sorbents, was obtained from the cones of European Spruce *(Picea abies).*

The aim of the work is to develop a solid dosage form with an adsorption activity based on a water-soluble polysaccharide complex from the cones of European Spruce *(Picea abies).*

Materials and methods. The samples of European Spruce *(Picea abies)* cones were collected on the territory of Ilyinsky district of the Perm Krai and used as plant raw materials. A water-soluble polysaccharide complex was obtained from the raw materials. In order to improve the technological properties of the substance, (WSPC) granulates were obtained. The granulates were hand-made by wet granulation. The adsorption activity of the obtained granules was determined by the ability to bind methylene blue.

Results. As a result of the experiment it has been established, that the WSPC substance of European Spruce *(Picea abies)* cones needs to be improved in its technological properties. Granulation of the substance led to an improvement in technological properties and an increase in the adsorption activity in most of the selected compositions. It has also been shown that increased moisture content of granulate decreases its adsorption activity. A direct dependence of the adsorption activity on the concentration of the granulating liquid (with the exception of some granulates) has been revealed, but no significant effect of the size of the granulate particles on the manifestation of the adsorption effect has been reported. According to the results of the study, a dosage form "Capsules" has been proposed for the compositions that showed the best results of the adsorption activity, and their biopharmaceutical evaluation was carried out according to the disintegration test.

Conclusion. Thus, a solid dosage form with an adsorption activity has been obtained. The study shows the prospects for further research on the preparation of the drug with an adsorption activity based on the water-soluble polysaccharide complex of European Spruce *(Picea abies)* cones.

Keywords: sorbents, capsules, water-soluble polysaccharide complex, European Spruce *(Picea abies)* cones, adsorption activity, granulation

РАЗРАБОТКА ТВЕРДОЙ ЛЕКАРСТВЕННОЙ ФОРМЫ С АДСОРБЦИОННОЙ АКТИВНОСТЬЮ

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Энтеросорбенты выпускаются в различных лекарственных формах – порошки, таблетки, пасты и др., также некоторые наименования встречаются в виде капсул. Из шишек ели обыкновенной получен водорастворимый полисахаридный комплекс (ВРПК), проявляющий выраженную адсорбционную активность, что обуславливает перспективы разработки лекарственных форм сорбентов.
Цель работы – разработка твердой лекарственной формы с адсорбционной активностью на основе водорастворимого полисахаридного комплекса ели обыкновенной шишек.
Материалы и методы. В качестве растительного сырья использовали образцы ели обыкновенной шишек, собранные на территории Ильинского района Пермского края. Из сырья был получен водорастворимый полисахаридный комплекс. С целью улучшения технологических свойств субстанции ВРПК были получены грануляты ВРПК. Грануляты получали вручную, путем влажного гранулирования. Адсорбционную активность, полученных гранулятов, определяли по способности связывать метиленовый синий.
Результаты. В результате эксперимента установлено, что субстанция ВРПК шишек ели нуждается в улучшении технологических свойств. Гранулирование субстанции привело к улучшению технологических свойств и увеличению адсорбционной активности у большинства выбранных составов. Так же показано, что при повышенной влажности гранулята понижается его адсорбционная активность. Выявлена прямая зависимость адсорбционной активности от концентрации гранулирующей жидкости, за исключением некоторых гранулятов, но существенного влияния размера частиц гранулята на проявление адсорбционного действия, не было выявлено. По результатам исследования предложена лекарственная форма «Капсулы» для составов, показавших наилучшие результаты адсорбционной активности, и проведена их биофармацевтическая оценка по тесту «Распадаемость».
Заключение. Таким образом, была получена твердая лекарственная форма с адсорбционной активностью. Проведенное исследование показывает перспективность дальнейших исследований по получению лекарственного средства с адсорбционной активностью на основе водорастворимого полисахаридного комплекса шишек ели.
Ключевые слова: сорбенты, капсулы, водорастворимый полисахаридный комплекс, шишки ели обыкновенной, адсорбционная активность, грануляция

INTRODUCTION

Enterosorbents are group of drugs with various structures that bind and remove exo- and endogenous substances from the gastrointestinal tract (GIT) by adsorption, absorption, ion exchange, complexation [1].

Herbal polysaccharides have many useful properties, including adsorption [2–4]. They are able to "bind" heavy metals, some groups of secondary metabolites despite their solubility in water. These interactions are complex and described not only by adsorption, but also by intermolecular interactions or their ability to complexation. In addition, the use of the term "water-soluble polysaccharides – WSPS" is often criticized, since it is clear that water educes a complex of substances during the extraction of plant materials. Therefore, the uses of this term is a tribute to traditions than a description of specific physicochemical interactions [2–5]. The aqueous solutions of pectin polysaccharides from rowanberry fruits exhibit pronounced antioxidant and antiradical activity [6, 7]. Polysaccharides of the aquatic plant *Brasenia schreberi* J.F. Gmel. exhibit pronounced antiradical activity [8]. The sorption properties of herbal polysaccharides are being studied, such as: pectin substances of peach and peach gum [9–11], apples and sunflower baskets [9]; herbal polysaccharide complexes from milk thistle, fruits of sweet-brier, seeds of pumpkin, watermelon, grape, walnuts [13]. Polysaccharides of yellow melilot exhibit anti-inflammatory [13], immunocorrecting [14, 15], antianemic and adaptogenic effects [16]. *Stipa parviflora* polysaccharides exhibit hepatoprotective activity in experiments *in vivo* [17]. Polysaccharides of *Psidium guajava* leaves exhibit hypoglycemic activity in a model of diabetes induced by streptozotocin [18].

Plant-based sorbents (including polysaccharides), while entering the small bowel are full or partially fermented by the gut microbiome. It is known that some sources of prebiotics (inulin, resistant starches and some oligosaccharides) acting as a selective substrate for bacteria, which produce specific short-chain fatty acids and can lower intestinal pH. Short-chain fatty acids stimulate the proliferation of epithelial cells, which can healing the damaged part of the colonic wall [19]. Due to the formation of short-chain fatty acids, polysaccharides promote the growth of gut microbiome *Bifidobacteria and Lactobacilli*, and also inhibit the growth of pathogenic microorganisms [2, 20]. This is the advantage of sorbents based on polysaccharides in comparison with other sorbents obtained from non-plant raw materials.

At the Department of Pharmacognosy with a course of botany of the Perm State Pharmaceutical Academy, a water-soluble polysaccharide complex with adsorption activity was obtained from raw materials of spruce cones. In the experiment WSPC of spruce cones showed high adsorption activity for their ability to bind methylene blue, which known as a marker for many sorbents. The adsorption activity of spruce cones WSPC (232.88±4.17) turned out to be better than activity of comparator drug – activated carbon (230.9±1.12) and silicon diox-

ОРИГИНАЛЬНАЯ СТАТЬЯ
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ide (211.5±1.42) [21]. The water-soluble polysaccharide complex of spruce cones exhibits high anti-inflammatory activity in the model of acute carrageenan edema caused by sub-plantar injection of 1% carrageenin solution into the rat's hind paw. The water-soluble polysaccharide complex of spruce cones reduced the increase of inflammatory edema by 65% compared to the control group, which is comparable to the activity of the comparator drug diclofenac sodium (68.3% inhibition of the inflammatory responses) [22].

The antioxidant activity has been established at the spruce cones' WSPC. The antioxidant activity was determined using a reaction with a stable radical – 2,2-diphenyl-1-picrylhydrazyl (DPPH). The IC50 value (the substance concentration which is bind a half of the concentration of the DPPH) for WSPC of spruce cones is 19.56 µg/ml and the same value for the comparator substance (ascorbic acid) is 9 µg/ml, which indicated the presence of antioxidant activity in the investigated substance [23].

Considering that fact, the development of a dosage form of WSPC is a relevant.

THE AIM of the work is to develop of solid dosage form in a capsule with adsorption activity based on a water-soluble polysaccharide complex from the cones of European Spruce.

MATERIALS AND METHODS

The object of the research is a water-soluble polysaccharide complex, which is an amorphous light-brown powder, after micronization, with a characteristic odor. WSPC from spruce cones was obtained by the method described by N.K. Kochetkov [24]. A weighed sample of the air-dry raw material was reduced up to a particle size 2 mm in diameter. A water-soluble polysaccharide complex of spruce cones was obtained by purified water extraction in a ratio of 1:10 at a temperature of 80°C for 1.5 hours. The obtained extracts were evaporated under vacuum and the sedimented by the triple addition of 95 percent alcohol. The polysaccharides were precipitated with alcohol, then were removed by filtration and purified by multiple washing with 95 percent ethanol. The drying was carried out in a hot air at a temperature of 60°C and grinding.

The samples of spruce cones were collected before seed ripening in July 2017, on the territory of the Ilyinsky District of the Perm region for obtaining a polysaccharide complex. The drying of samples was carried out by a shade-drying method. The prepared and dried samples corresponded to the requirements of the State Pharmacopoeia of the XIV^{ed} on the next terms: essential oil, tannins and extractives (by water) [24].

In order to improve the technological properties of the WSPC, the granulate were obtained. The WSPC granulates of Spruce cone were obtained by wet granulation. Wet granulation was carried out by hand made on the next methodology: a weighed sample of the WSPC powder was weighed of an electronic analytic balance and placed in a mortar; the liquid for granules was weighed with cylinder. The powder was moistened by gradually adding the liquid for granulates and mixing. Then the mass of moistened granules was rubbed through a wire-mesh screen with the mesh size of 1 mm and 0.5 mm. The obtained granules were thinly spread over paper on a metal tray and dried in a drying at temperature of 60°C for 2 hours.

Determination of the technological properties of substance and the granulates was carried out according to the methods presented in the State Pharmacopoeia of the Russian Federation XIV^{ed} [25]: the flowability, the tapped density (weight), the powder compression, the moisture content.

The Latin square method to select the required rational composition, as a mathematical planning, was used [26]. The factors, that will affect the adsorption activity, were: the aqueous factor of granulates liquids (factor A): A1 – agar-agar; A2 – sodium alginate; A3 – methyl cellulose; A4 – pectin; concentration of granulates liquid (factor B): B1 – 1%; B2 – 5%; moisture content of the obtained granulate (factor C): C1 – from 6% to 8%; C2 – over 8%, granulate particle size (factor D): D1 – 1 mm; D2 – 0.5 mm, filler in the granutable mixture (factor E): E1 – without a filler; E2 – with the filler (lactose).

The sorption activity is determined by the ability to bind a substance and methylene blue by the method of V.I. Reshetnikov [27]. About 0.2 g of polysaccharides or granulates (accurately weighed) were placed in a 250 ml conical flask, 50 ml of 0.15% methylene blue solution was added, and mixed in a laboratory shaker with 140 vibrations per minute for 1 hour. The separation of the ratio solution after sorption was carried out by during centrifugation at 8000 rpm. One milliliter of the supernatant was placed into a 500 ml capacity measuring flask and made up to the mark by purified water. Next, the optical density on the SP 2000 spectrophotometer at 664 nm in a cuvette with a 10 mm layer thickness was measured. Purified water was used as a comparator solution. The index of sorption activity was calculated according to formula:

$$X = \frac{(A_0 - A) \times a \times 50}{A_0 \times b \times (1 - 0,01 \times W)},$$

where:

A_0 – optical density of reference standard methylene blue;

A – optical density of test solution;

a – the actual concentration of reference standard methylene blue, mg/ml;

b – the weighment of substance, g;

50 – the volume of reference standard methylene blue, ml;

W – the moisture content of substance, %.

The disintegration test was made on "Rotating Basket" ERWEKA ZT 223 apparatus by the basket method [24]. The eighteen samples of filled capsules were placed in each of the 6 tubes. Then the basket was put down into a vessel with water temperature of 36°C, then turned on the apparatus and noted the time. After 30 minutes, the basket was removed and the conditions of the capsules was examined. All samples must disintegrate. Not less than 16 out of 18 samples must disintegrate completely.

For part samples, the disc-based method was used – in these cases, a disc was placed on each of the six samples before determination was started. The disk method is identical the basket method.

The sample was considered completely disintegrated when there is no residue or the residue was a soft mass that collapsed with a light touch of a glass rod, apart from fragments of the insoluble capsule shell, which are on the reticle or adhered to the lower surface of the disk.

Seven replicate measurements were made. statistical manipulation was carried out according to GPM.1.1.0013.15 SP XIV^{ed} "Statistics of the chemical experiment results. The *p*-value and Student *t*-test were calculated by the Microsoft Excel.

RESULTS AND DISCUSSION

The technological properties were researched and were obtained the following characteristics for assess the possibility of uses a solid dosage form (capsules), the result presented in Table 1.

The most important value of powder encapsulation process is flowability, because hard gelatin capsules filling and dosing by volumetric method. As shown in Table 1, the substance of WSPC doesn't have the capability for free poured out of the funnel under the gravity force (flowability). The vibration didn't have significance improvement of the score (Carr index = 22.78%, Hausner's ratio = 1.30). The value of the angle with natural repose of the substance also has turned out to be higher than recommended value (36–45°). It was found that the values of determined tapped density are lower than his specification limits. In this way, conducted researches has shown that the technological characteristics of substance WSPC are unsatisfactory: flowability (with and without vibration), angle of repose and tapped density. In this regard, in the future development of composition and technology an encapsulated dosage form with substance WSPC will be necessary to improve technological properties of this substance by adding excipients and using different technological methods (for example, wet granulation).

It is known that the transformation a powdery material into particles of a certain size (granulation) has a positive effect on the flowability. The classical method of granulation is compacting of powder particles by a binder (agar-agar, sodium alginate, methyl cellulose, pectin) and the next drying (wet granulation). In order to improve the flowability of the WSPC a row of granules in combinations with various excipients were obtained.

It is also known that the one of most important quality attribute of dry medicines from medicinal plant raw materials is moisture content. This quality attribute has a significant effect on different indicators: the stability of the drug, quantitatation, technological properties, such as flowability and tapped density, adsorption activity. A significant quantity of moisture can significantly reduce adsorption activity on surface and inside the raw material.

Therefore, for each granules, were researched technological properties, also the moisture content and adsorption activity were determined.

The results of research moisture content and adsorption activity of the granules are presents in Table 2.

As a result, it was found that the granulation by the wet granulation led to an increase of adsorption activity of most selected compositions, with the exception of compositions No.1 and No.3. The greatest adsorption activity from the granulates compositions No.1–8 was shown by the granulates No.8. The results of Table 2 shown that the granulates moisture content was confirmed on adsorption activity. The moisture content of the granulates increases that leads adsorption activity decreases, which can be explained by a decrease in the sorption capacity of granulates due to binding with water molecules. Considering this, the next granulates were obtained with a moisture content not more than 8% (factor C).

A direct dependence of the adsorption activity from the concentration of granulation liquid (factor B) was also revealed (the exception is granules No 4 and No 5). According to the results in Table 2, granulation liquids for next research were selected: sodium alginate, methyl cellulose and pectin at 5 percent concentration. Compositions granulated with agar-agar were excluded from next researches due to its low adsorption activity (1 percent solution) and a difficult granulation process (5 percent solution).

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In order for next research to granutable WSPC is added lactose, for optimally adjustment of technological properties. Lactose is a known such as excipient of the disaccharide group, widely used in solid dosage form technology. After preliminary studies of the technological properties of granutable WSPC and lactose in different correlations, an optimal ratio of 9:1 (WSPC/lactose) was proposed [27].

The technological properties of compositions and their adsorption activity were researched.

The influence of factors A (type of granulation liquid), B (concentration of granulation liquid), D (particle size of granules), E (presence or absence of lactose) on the adsorption activity of granulates was studied. The results of adsorption activity were rated with the initial WSPC substance and activated carbon powder. The activated carbon was used as a reference drug as a well-known drug with a broad-spectrum of action.

The results of the researches of granulation liquid, moisture content and particle size's influence on the technological properties of WSPC granulates and lactose are presented in Table 3.

According to the results of the researches, it was found that all granules (No.9–No.11) have next technological properties: satisfactory flowability with an acceptable angle of repose (Hausner's ratio 1.09–1.19; Carr index is 8.94–16.49 percent) and a fairly high tapped density.

After analyzing the results of Table 3, was noticed: a decrease of the particle size to 0.5 mm (No 10 and No 12) is led to insignificant changes in technological properties, in comparison with particle size granulates which has a of 1 mm (No.9, No.11, No.13) and had practically no effect in the initial technological properties of the WSPC substance. Thus, it was concluded that the particle size of granulates the in the range from 0.5 to 1.0 mm does not have significantly affect on technological properties of those granulates.

It was also found that the type of granulation liquid and the presence of lactose in granules doesn't change the technological properties of the test granulates (Table 4).

During the research of adsorption activity for test granulates (No.9 – No.11), some conclusions was established. Following from the results of Table 4, when lactose is added to the granutable mixture, the adsorption activity of the granulate increases, with the exception of granules of composition No.11, No.12. The change of the particle size didn't have any dependence reveal, since the adsorption activity of granulates No.13, No.14, No.11, No.12 decreases with decreasing particle size, and the adsorption activity of granulates No.9, No.10 increases with decreasing particles. The dependence an adsorption activity from particle size was established, for nextresearches.

For the development of a solid dosage form with adsorption activity, literature data was taken into account. It is known that there is a number of problems in the development of solid dosage forms with high adsorption activity. In case of using sorbents, there is no release and absorption into biological matrix of any active principle. Another singularity of sorbents is the possibility of partial or complete inactivation of pharmacologically active ingredient during the preparation of a dosage form, depending on a number of factors: heating or contact with excipients and solvents, physical impacts, dehydration, creation of protective coverings, etc. [28]. Considering the forgoing, hard gelatin capsules were chosen for the development of a solid dosage form. The advantage of capsules over other solid dosage forms (for example, tablets) is the reduction of technological stages, because there is no tabletizing (pressing) stage, where physical impacts are required, often leading to a decrease of the substance adsorption activity.

For filling, we chose STANDARD gelatin capsules of typical size 0 with a filling volume of 0.68 ml [29]. The large typical size of the capsules was chosen with the concideration of the expected dosage of the WSPC substance.

The capsules were filled with granulates No.9, No.10, No.11, No.12, No.13, No.14 by volumetric method. The disintegration of the obtained dosage form was determined according to the State Pharmacopoeia [25]. The test was carried out with the "Rotating Basket" apparatus with and without discs. The results are presented in Table 5.

In the course of research, it was found that factors A (granulation liquid) and D (granulate particle size) have a direct effect on the capsule's ability to disintegrate in a defined time (not more than 30 minutes). From the results presented in table 5, it can be seen that the capsules filled with granulate No.12 have disintegrated in 25 minutes according to the method without discs, capsules with granulates No.13, No.14, No.11, No.9, No.10 – in more than 30 minutes. To improve the indicators of the "Disintegration" test the method with discs was applied. According to the method with discs, the capsules with granulate № 12 have disintegrated in 18 minutes, with granulate № 10 – in 27 minutes, which corresponds to the defined time.

In further researches, it is possible to use the method with discs. Thus, the best results of the Disintegration test were obtained using a granulation liquid – methyl cellulose solution with a granulate particle size of 0.5 mm.

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PHARMACY & PHARMACOLOGY

Table 1 – The technological properties of the WSPC

Object	Moisture content, %	Flowability, g/s		Angle of repose, °	Tapped density, kg/m³		Hausner's ratio	Carr index
		Without vibration	With vibration		Bulk density (untapped)	Tapped density (tapped)		
WSPC	8.2	None	2.74±0.2	51	569.69±3.56	737.83±2.26*	1.30	22.78
Reference values	–	3.0–6.5		36–45	>600	> 600	1.19–1.25	16–20
Compliance with reference values	–	Not compliant	Not compliant	Not compliant	Not compliant	Compliant	Not compliant	Not compliant

Note: * $p \geq 0.001$ – compared to the sample before compaction

Table 2 – The influence of granulation liquid concentration and moisture content on the adsorption activity of granulates

No.	Object	Moisture content, %	Adsorption activity, mg/g $\bar{x} \pm \Delta\bar{x}$
1	WSPC	8.2	180.03 ± 0.88
2	Activated carbon powder	7.8	232.64±0.51
3	No.1 – $A_1B_1C_1D_1E_1$	8.5	112.28±0.54
4	No.2 – $A_1B_2C_1D_1E_1$	9.7	195.91±0.85**
5	No.3 – $A_1B_2C_2D_1E_1$	18.3	94.13±0.52
6	No.4 – $A_2B_1C_1D_1E_1$	7.3	221.91±0.51**
7	No.5 – $A_2B_2C_1D_1E_1$	7.5	192,25±0.91**
8	No.6 – $A_3B_1C_1D_1E_1$	6.6	191.41±0.41**
9	No.7 – $A_3B_2C_1D_1E_1$	7.2	215.44±0.76**
10	No.8 – $A_4B_2C_1D_1E_1$	7.7	266.95±0.83*

Note: * – accurate with a confidence range $p \geq 0.001$ compared with activated carbon powder; ** – $p \geq 0.001$ compared with WSPC

Table 3 – The influence of granulation liquid, moisture content and particle size on the technological properties of WSPC granulates with lactose (9:1)

No.	Object	Particle size, mm	Moisture content, %	Flowability with vibration, g/s	Angle of repose, °	Tapped density, kg/m³		Hausner's ratio	Carr index, %
						Bulk density (untapped)	Tapped density		
1	WSPC	1.0	8.2	2.74±0.2	51	569.69±3,56	737.83±2.26	1.30	22.78
2	No.9 – $A_4B_2C_1D_1E_2$	1.0	7.3	8.47±0.82*	35	537.72±2,89	590.54±2.34	1.09	8.94
3	No.10 – $A_4B_2C_1D_2E_2$	0.5	7.3	7.44±0.39*	40	575.16±3.04***	662.30±2.58***	1.15	13.16
4	No.11 – $A_3B_2C_1D_1E_2$	1.0	6.8	6.02±0.30*	60	458.45±3.25	529.80±2.19	1.16	13.47
5	No.12 – $A_3B_2C_1D_2E_2$	0.5	7.4	5.03±0.79**	40	488.24±2.97***	578.14±2.47***	1.18	15.50
6	No.13 – $A_2B_2C_1D_1E_2$	1.0	6	7.16±0.54*	38	481.60±3,16	542.38±2.32	1.12	11.20
7	No.14 – $A_2B_2C_1D_2E_2$	0.5	6	6.10±0.42*	40	511.50±3.05***	612.54±2,28***	1.19	16.49
8	Reference values	–	–	3.0–6.5	36–45	> 600	> 600	1.19–1.25	16–20

Note:* – accurate with a confidence range $p \geq 0.001$ compared with WSPC; ** – $p \geq 0.05$ compared with WSPC; *** – $p \geq 0.001$ compared with the particle size of 1 mm

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Table 4 – The influence of granulation liquid, moisture content and particle size on the adsorption activity of WSPC granulates with lactose (9:1)

No.	Object	Partical size, mm	Moisture content, %	Adsorption activity, mg/g $(\bar{x}\pm\Delta\bar{x})$
1	WSPC	1	8.2	180.03±0.88
2	Activated carbon powder	1	7.8	232.64±3.12
3	No.9 – $A_4B_2C_1D_1E_2$	1	7.3	215.73±0.43*
4	No.10 – $A_4B_2C_1D_2E_2$	05	7.3	271.54±0.10**
5	No.11 – $A_3B_2C_1D_1E_2$	1	6.8	150.80±0.84
6	No.12 – $A_3B_2C_1D_2E_2$	05	7.4	115.66±0.74**
7	No.13 – $A_2B_2C_1D_1E_2$	1	6.0	250.58±0.95*/***
8	No.14 – $A_2B_2C_1D_2E_2$	05	6.0	232.70±0.94*

Note: * – accurate with a confidence interval p≥0.001 compared with WSPC; ** – p≥0.001 compared with the particle size of 1 mm; *** – p≥0.001 compared with the particle size of 0.5 mm

Table 5 – The results of the "Disintegration" test of capsules filled with WSPC granulates with lactose (9:1)

No.	Object	Particle size, mm	Disintegration, min	
			Without disks	With disks
1	No.13 – $A_2B_2C_1D_1E_2$	1	> 30	–
2	No.14 – $A_2B_2C_1D_2E_2$	0.5	> 30	–
3	No.11 – $A_3B_2C_1D_1E_2$	1	> 30	–
4	No.12 – $A_3B_2C_1D_2E_2$	0.5	25	18
5	No.9 – $A_4B_2C_1D_1E_2$	1	> 30	–
6	No.10 – $A_4B_2C_1D_2E_2$	0.5	> 30	27

CONCLUSION

The WSPC substance of spruce cones has been obtained and technological properties (flowability with and without vibration, angle of repose, bulk and tapped density, Carr index and Hausner's ratio) have been determined in laboratory conditions.

The granules of spruce cones WSPC and compositions with lactose in ratio (9:1) have been obtained under laboratory conditions with granulation liquids: agar-agar, sodium alginate, methyl cellulose, pectin in various concentrations with particle sizes of 1 mm and 0.5 mm and moisture content from 6 percent and higher. A total amount of 14 granules have been obtained. The technological properties (flowability, angle of repose, bulk and tapped density, Carr index and Hausner's ratio), adsorption activity of the granules and the dependence of these indicators from the factors of the granulation process have been determined.

The capsules with granules of a composition WSPC spruce cones with lactose (9:1) have been obtained and the «Disintegration test» of dosage form was carried out in laboratory conditions.

According to the disc – method, capsules with granules of two compositions have been shown a satisfactory result.

The studies of factor A have shown that pectin has become a promising granulating liquid

Thus, after researches and validation of results, the optimal composition for encapsulation to hard gelatin capsules STANDARD of typical size 0 has been chosen: the spruce cones WSPC substance and lactose in a ratio at 9:1; as a binding liquid was used 5% pectin with moisture content of no higher than 8% and a particle size of 0.5 mm, which can be used for next researches in the development of a new herbal medicine with high adsorption activity.

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CONFLICT OF INTERESTS

The authors declare no conflicts of interests.

AUTHOR'S CONTRIBUTIONS

All authors have contributed to the research equally.

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