



DEVELOPMENT OF PERORAL HYPOLIPIDEMIC FORMULATION BASED ON SULFATED ARABINOGLACTAN IN THE FORM OF POTASSIUM SALT

Ya.A. Kostyrov¹, K.V. Alekseev²

¹ Federal State Budget Institution for Science "A.E. Favorsky Irkutsk Institute of Chemistry Siberian Branch of the Russian Academy of Sciences"

1, Favorsky St., Irkutsk, Russia, 664033

² Federal State Budgetary Institution "Research Zakusov Institute of pharmacology"

8, Baltyskaya St., Moscow, Russia, 125315

E-mail: yanakos@irioch.irk.ru

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An original heparinoid, sulfated arabinogalactan in the form of potassium salt, possessing anticoagulant and hypolipidemic activities, has been developed at the A.E. Favorsky Irkutsk Institute of Chemistry Siberian Branch of the Russian Academy of Sciences.

The aim was to develop solid peroral dose forms (capsules and film-coated tablets) for the prevention and treatment of atherosclerotic lesion of blood vessels on the basis of potassium salt of sulfated arabinogalactan which would be suitable for further clinical trials of these forms.

Materials and methods. The following materials were used in the work: sulfated arabinogalactan in the form of potassium salt, obtained at the A.E. Favorsky Irkutsk Institute of Chemistry Siberian Branch of the Russian Academy of Sciences; Ludi-press®; AEROSIL® 200 Pharma; calcium stearate; Aquacoat ECD. The powder mixtures were briquetted followed by tableting and application of the finished film coating Aquacoat ECD, and encapsulation in hard gelatin capsules.

Results. Composition and technological characteristics of capsules and film-coated tablets were determined using physico-chemical and technological properties of sulfated arabinogalactan in the form of potassium salt. Technological parameters and quality indicators were determined for the solid pharmaceutical dose forms in accordance with the requirements of the State Pharmacopoeia of the Russian Federation of the XIVth edition.

Conclusion. The optimum compositions and technology for the preparation of capsules and film-coated tablets based on potassium salt of sulfated arabinogalactan for the prevention and treatment of atherosclerotic lesion of blood vessels, were developed. The data obtained were used for the regulatory documentation design.

Keywords: sulfated arabinogalactan; film-coated tablets; capsules; production technology

Abbreviations: RF – the Russian Federation; SB RAS – Siberian Branch of the Russian Academy of Sciences; FDF – finished dosage form; GPhM – General Pharmacopoeial Monograph; FFC – finished film coating.

РАЗРАБОТКА ПЕРОРАЛЬНОЙ ЛЕКАРСТВЕННОЙ ФОРМЫ ГИПОЛИПИДЕМИЧЕСКОГО ДЕЙСТВИЯ НА ОСНОВЕ СУЛЬФАТИРОВАННОГО АРАБИНОГАЛАКТАНА В ВИДЕ КАЛИЕВОЙ СОЛИ

Я.А. Костыров¹, К.В. Алексеев²

¹ Федеральное государственное бюджетное учреждение науки «Иркутский институт химии имени А.Е. Фаворского» Сибирского отделения Российской академии наук
664033, Россия, г. Иркутск, ул. Фаворского, д. 1

² Федеральное государственное бюджетное научное учреждение
«Научно-исследовательский институт фармакологии им. В.В. Закусова»
125315, Россия, г. Москва, ул. Балтийская, д. 8

E-mail: yanakos@irioch.irk.ru

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В Иркутском институте химии им. А.Е. Фаворского Сибирского отделения Российской академии наук разработан оригинальный гепариноид – сульфатированный арабиногалактан в виде калиевой соли, обладающий антикоагулянтной и гиполипидемической активностями.

Цель. Создание на основе сульфатированного арабиногалактана в виде калиевой соли твердых дозированных лекарственных форм для перорального применения в виде таблеток, покрытых пленочной оболочкой, и капсул для профилактики и лечения атеросклеротического повреждения кровеносных сосудов, которые в дальнейшем будут пригодны для клинического исследования.

Материалы и методы. Для получения твердых дозированных лекарственных форм использовались: сульфатированный арабиногалактан в виде калиевой соли, полученный в Иркутском институте химии им. А.Е. Фаворского СО РАН; Ludipress®; AEROSIL® 200 Pharma; кальция стеарат; Aquacoat ECD. Применялось брикетирование порошковых масс с последующим таблетированием и нанесением готового пленочного покрытия Aquacoat ECD и капсулирование в твердые желатиновые капсулы.

Результаты. На основе изученных физико-химических и технологических свойств сульфатированного арабиногалактана в виде калиевой соли обоснован состав и технология производства таблеток, покрытых пленочной оболочкой, и капсул. Для разработанных твердых дозированных лекарственных форм определены технологические параметры и показатели качества в соответствии с требованиями Государственной фармакопеи РФ XIV издания.

Заключение. Разработаны оптимальные составы и технологии получения таблеток, покрытых оболочкой, и капсул на основе сульфатированного арабиногалактана в виде калиевой соли для профилактики и лечения атеросклеротического повреждения кровеносных сосудов. Полученные данные положены в основу разработки нормативной документации.

Ключевые слова: сульфатированный арабиногалактан; таблетки, покрытые пленочной оболочкой; капсулы; технология производства

Список сокращений: РФ – Российская Федерация; СО РАН – Сибирское отделение Российской академии наук; ГЛФ – готовые лекарственные формы; ОФС – общая фармакопейная статья; ГПК – готовое пленочное покрытие.

INTRODUCTION

Atherosclerotic lesion of blood vessels is one of the most widespread and serious disorders of the homeostatic system. The use of drugs with a polyvalent mechanism of pharmacological action for the prevention and treatment of this pathology is justified, and the application of heparinoids for this purpose is very promising [1–8].

Foreign hypolipidemics based on natural and semi-synthetic heparinoids are limited [9–13] due to their physico-chemical properties (they are extremely easily destroyed in the digestive tract that impairs their absorption and transport to blood)¹.

In the Russian Federation (RF), heparinoids are represented by sulodexide-derived drugs, which exert angioprotective, profibrinolytic and antithrombotic effects². Sulodexide is an organopreparation, extracted from the mucous membrane of the small intestine of a pig. It is a natural mixture of glycosaminoglycans (80% of heparin-like fraction with a molecular weight of 8 kDa and 20% of dermatansulfate) [14–15]. The effective application of Sulodexide for the secondary prevention of coronary atherosclerosis and its complications is proven by clinical multicenter placebo-controlled trials [16–18]. Sulodexide-based medicines cause serious side effects in view of the peculiarities of the technology for obtaining

organopreparations. For instance, these drugs contain trace proteins and histamine-like substances that can lead to allergic reactions³.

Thus, the search for heparinoids devoid of similar disadvantages is an urgent problem in medical and pharmaceutical sciences.

A directed chemical modification of arabinogalactan, the main polysaccharide of Siberian larch, made it possible to develop the original pharmacologically active compound – sulfated arabinogalactan in the form of potassium salt (Agsular®), in A.E. Favorsky Irkutsk Institute of Chemistry Siberian Branch of the Russian Academy of Sciences⁴. This is a semi-synthetic heparinoid exhibiting anticoagulant and hypolipidemic activities, having a high relative bioavailability after the peroral administration (54.4%) [19]. The improved technology for the synthesis of potassium salt of sulfated arabinogalactan made it possible to obtain a pharmaceutical grade substance [20, 21]. The safety and efficiency of the latter has been proven by the pre-clinical trials conducted together with the Research Institute of Toxicology (St. Petersburg) in 2009–2011 [22, 23].

Thus, sulfated arabinogalactan in the form of potassium salt is a promising building block for the development of peroral medicines. Today, the most popular are such peroral finished dose forms (FDFs) as tablets and capsules, which have a wide range of possibilities and advantages [24–25].

¹ Ryzhenkov VE, Makarov VG, Remezova OV, Makarova MN. Metodicheskie rekomendatsii po izucheniyu gipolipidemicheskogo i antiskleroticheskogo dejstviya lekarstvennykh sredstv. [Methodical recommendations for the study of hypolipidemic and antisclerotic action of drugs]. In: Vol. 1, Rukovodstvo po provedeniyu doklinicheskikh issledovaniy lekarstvennykh sredstv. [Guidelines for conducting preclinical studies of drugs]. Moscow: Grif and K; 2012. p. 445–452. Russian

² State Register of Medicines of the Russian Federation. Available from: <http://grls.rosminzdrav.ru/Default.aspx>

³ Yakovlev VB, Zolotukhin SI. Great Medical Encyclopedia. Moscow: Soviet encyclopedia. 1981; 17: 392. Russian

⁴ A.E. Favorsky Irkutsk Institute of Chemistry Siberian Branch of the Russian Academy of Sciences, assignee. Agsular®. Russian Federation trademark No. 398618. 2010 Jan 19. Russian

THE AIM was to develop solid peroral dose forms (capsules and film-coated tablets) for the prevention and treatment of atherosclerotic lesion of blood vessels, on the basis of potassium salt of sulfated arabinogalactan which would be suitable for further clinical trials of these forms.

MATERIALS AND METHODS

Materials

The following materials were used in the work: sulfated arabinogalactan in the form of potassium salt (Ag-sular®), obtained according to the developed methods [20, 21]; Ludipress® (BASF, Germany); colloidal silicon dioxide – AEROSIL® 200 Pharma (Evonik Degussa, Germany); calcium stearate, analytically pure, reagent grade (Technical conditions 2432-061-56856807-04); Aquacoat ECD (FMC, USA); purified water (Pharmacopoeia Monograph.2.2.0020.18)⁵.

Study of physico-chemical properties

The shape and size of the particles were determined by scanning electron microscopy using a SEM 525-M scanning electron microscope (Philips, the Netherlands) and by dynamic light scattering using a Zetasizer Nano ZS analyzer (Malvern Instrument, UK). The measurements were carried out at the angles of 13° and 173° in plastic cuvettes (1×1 cm). The average hydrodynamic diameter was calculated by the analysis of fluctuations in the intensity of light scattering of spherical particles. The results were processed using the Dispersion technology Zetasizer family software v7.01.

The mass-average molecular mass was determined by high performance size exclusion chromatography on an Agilent 1260 Infinity chromatograph (Agilent Technologies, Germany), a PL aquagel-OH 408 nm column, 300×7.5 mm, a refractometer detector, a sample concentration of 1 mg/ml, a sample volume of 20 µL. The elution was carried out with a 0.1 M aqueous solution of lithium nitrate (LiNO₃) at 30°C with the eluent flow rate of 1 ml/min. The column was calibrated using D-galactose and dextrans with molecular weights of 5, 12, and 25 kDa (Sigma, United States). The calculations were performed using the Agilent ChemStation software.

The elemental analysis was performed on a Flash2000 automatic elemental analyzer (Thermo Scientific, Italy).

The solubility was determined according to the method described in General Pharmacopoeial Monograph (GPhM) 1.2.1.0005.15 "Solubility"⁶.

The average density (ρ_{av} , kg/m³) was determined by the ratio of the sample mass ($m \geq 0.3$ kg) to the entire volume occupied by it (V) in natural conditions, including

the cavities and pores in it (V_{pore}), and calculated by the formula:

$$\rho_{av} = \frac{m}{V} = \frac{m}{V_{s.ph.} + V_{pore}}, \quad (1)$$

where: ρ_{av} is an average density, kg/m³; m is the mass of the sample, kg; V is the sample volume, m³; $V_{s.ph.}$ is a volume of a solid phase, m³; V_{pore} is a volume of cavities and pores, m³.

Specific surface area ($S_{sp.s.}$, m²/kg) was determined as the sum of the surface of all particles, the total mass of which was 1 kg, and calculated by the formula:

$$S_{sp.s.} = \frac{k}{d_{s.ph.} \times \rho_{av}}, \quad (2)$$

where: $S_{sp.s.}$ is a specific surface area, m²/kg; k is a particle shape factor; $d_{s.ph.}$ is a particle diameter of the solid phase, m; ρ_{av} is an average density, kg/m³.

The hygroscopicity (H , %) was determined under the extreme conditions (in a chamber with a relative humidity of 100% for 24 hours) [26]. The kinetics of the moisture absorption was calculated by the formula:

$$H = \frac{(m - m_0) \times 100\%}{m}, \quad (3),$$

where: H is a hygroscopicity, %; m_0 is the mass of the powder before being kept in a chamber with a 100% air humidity, g; m is the mass of the powder after the exposure in the chamber with a 100% air humidity, g.

Study of technological properties

A fractional (granulometric) composition was determined according to the method described in GPhM.1.1.0015.15 "Sieve analysis"⁷ on an automatic WEB scatterer (MLW-Labortechnik, Germany).

The flowability (g/s), the angle of repose (°) and the bulk density (g/ml) were determined according to the methods described in GPhM.1.4.2.0016.15 "The degree of flowability of powders"⁸ on a device for determining the flowability TK-1 (Pharmatech, Ukraine) and on a device for vibration compaction of powders 545-P-AK-3 (Pharmatech, Ukraine).

The compressibility (breaking strength, N) was determined according to the following procedure: a weighed portion (0.3 g) of the powder was compressed in a matrix with a diameter of 9 mm on a PGR 400 manual hydraulic press (Infraspek company, Russia) at the pressure of 120 MPa. After pushing the tablet out of the matrix, the compressive strength was determined using a tablet and granule strength tester TT-03 (China) in kg of load, which was recalculated in N [26].

The Hausner index was calculated by the formula:

⁵ State Pharmacopoeia of the Russian Federation XIV ed., Vol. I–IV. Available from: <http://femb.ru/pharmacopea.php>

⁶ Ibid.

⁷ Ibid.

⁸ Ibid.

$$Hausner_{index} = \frac{\rho_{bd1}}{\rho_{bd0}}, \quad (4),$$

where: ρ_{bd0} is a bulk density before the compaction, kg/m³; ρ_{bd1} is a bulk density after the compaction, kg/m³ [27].

The Carr index (%) was calculated by the formula [28]:

$$Carr_{index} = \frac{100\% \times (\rho_{bd1} - \rho_{bd0})}{\rho_{bd1}}, \quad (5),$$

where: ρ_{bd0} is a bulk density before the compaction, kg/m³; ρ_{bd1} is a bulk density after the compaction, kg/m³.

Technology for tablets production

Briquetting was carried out from a powder mixture of active ingredients and auxiliary substances obtained in a PSM "plough" mixer (Pharmag, Germany) at 50-250-450 rpm for 30 min, on a hydraulic hand press PGR 400 (matrix diameter – 25 mm) (Infraspek company, Russia) under the pressure of 200 bar. The briquettes were grinded in a dry granulator DG (Pharmag, Germany).

The obtained granules were fractionized on an automatic diffuser (WEB MLW-Labortechnik, Germany); for tableting, granules with a size of at least 1 mm were used.

Tableting was performed using the punches to the tablet press CPR-6 (Dott. Bonapace & C s.r.l., Italy), allowing biconvex tablets with a diameter of 12 mm to be obtained.

The application of 30% aqueous dispersion of the finished film coating Aquacoat ECD was performed in a CP-9 coater (Pharmag, Germany) with a fixed operating angle of the device (45°). The coated tablets were dried using infrared light (150 W).

Technology for capsules production

The encapsulation was carried out using the finished semi-closed hard-gelatin capsules Empty Hard Gelatin Capsules (Shaanxi Genex Bio-Tech Co., Ltd., China) with the sizes No. 00-1. The capsules were filled with the help of manual machines MC-1.2 (Multipharma, Italy) of the appropriate size.

FDF quality assessment

The quality of the obtained FDFs was evaluated according to the standard pharmacopoeial methods⁹:

1. GPhM.1.4.2.0009.15 "Uniformity of the mass of dosage forms", the determination of the uniformity of the mass of the capsules contents, was carried out using laboratory electronic scales LV 120-A (Sartogsm, Russia);

2. GPhM.1.4.2.0008.15 "Dosage Uniformity", the determination of the distribution uniformity of the active substance among individual dosage units of FDFs (capsules and film-coated tablets) was carried out according to method 2 using laboratory electronic scales LV 120-A (Sartogsm, Russia);

3. GPhM.1.4.2.0013.15 "Disintegration of tablets and capsules", the determination of disintegration, was carried out in purified water using the laboratory identifier of the disintegration process 545 AK-00-00 (Pharmatech, Ukraine).

4. GPhM.1.4.2.0014.15 "Dissolution for solid dosage form", the determination of the amount of active substance released from the pharmaceutical dose forms for a certain period of time, was carried out in purified water using a device for determining the solubility 545 AK7-00-00 (Pharmatech, Ukraine) by spectrophotometric method on a UV/VIS spectrometer Lambda 35 (Perkin Elmer, USA).

5. GPhM.1.4.1.0015.15 "Tablets", the determination of the excipients amount aerosil and calcium stearate) was carried out by the gravimetric method using laboratory electronic scales LV 120-A (Sartogsm, Russia).

Statistical processing of results

All obtained data were statistically processed (P = 95%) using the Student's test in accordance with the requirements of GPhM.1.1.0013.15¹⁰.

RESULTS AND DISCUSSION

Physico-chemical and technological properties

The most economically beneficial and technological method for tableting of powders is their direct compression. However, despite the advantages of this method, it is applicable for a limited number of pharmaceutical substances and depends on their physico-chemical and technological properties [29].

Sulfated arabinogalactan in the form of potassium salt (Fig. 1) is a hydrophilic functionalized biopolymer, where sulfate groups are located at the C2 and C4 atoms of the main galactan chain and at the C6 atom of the terminal galactose residues of the main and side chains of the polysaccharide. According to the data of elemental analysis and characteristics of the molecular weight distribution, the degree of substitution of the macromolecule is 0.4, i.e. about one sulfate group is per one structural unit of the biopolymer [21].

⁹ Ibid.

¹⁰ Ibid.

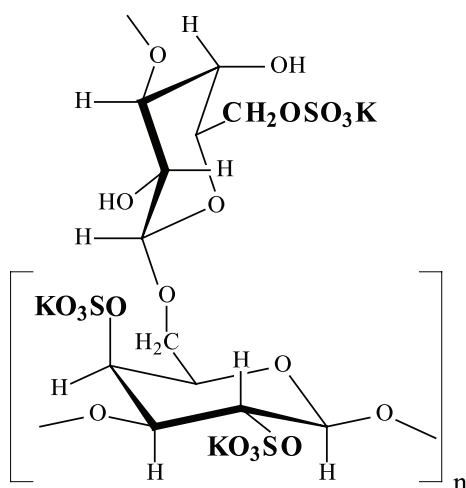


Figure 1 – Fragment of sulfated arabinogalactan in the form of potassium salt

Visually, it is a white or white-creamy amorphous powder with a weak characteristic odor. According to the data of scanning electron microscopy (Fig. 2A), its particles have a spherical shape and form large agglomerates with the size in the range of 200-600 nm (Fig. 2B).

To evaluate suitability of a sulfated arabinogalactan potassium salt for tableting by direct compression methods, its physico-chemical (Table 1) and technological properties (Table 2) were studied.

The results of the carried out experiments showed that sulfated arabinogalactan in the form of potassium salt is finely dispersed amorphous powder with high hygroscopicity (20.07%). It is almost uniform in the particle size distribution, which does not meet the requirements to powders for direct pressing, since it has low technological properties.

Powders with a particle size of 0.5–1 mm are known to be the best for a direct compression [24]. This parameter for sulfated arabinogalactan in the form of potassium salt is only 8.6%, and the amount of the fine fraction is more than 79%. That significantly affects the material flowability, leading to its almost complete

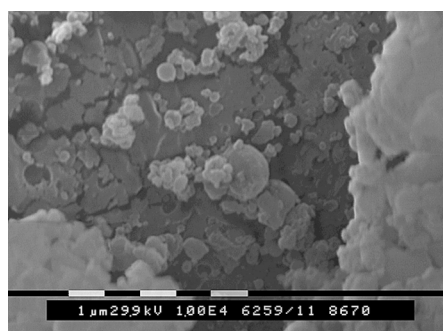
absence (1 g/s). In this case, not the entire sample spilled out by gravity from the device funnel, there was a partial freezing, dusting and static-charge accumulation of the powder. The Carr (24.91%) and the Hausner (1.33) indices confirm a very poor compressibility (24.5 N) of sulfated arabinogalactan in the form of potassium salt, accompanied by the complexity of filling the matrix and ejecting the finished tablet from it. All these can lead to a violation of the active substance dosage accuracy in the FFC.

In this regard, the next stage was to bring technological properties of sulfated arabinogalactan in the form of potassium salt into compliance with the properties of a technologically conditioned mass, suitable for obtaining tableted FFC by the direct compression method.

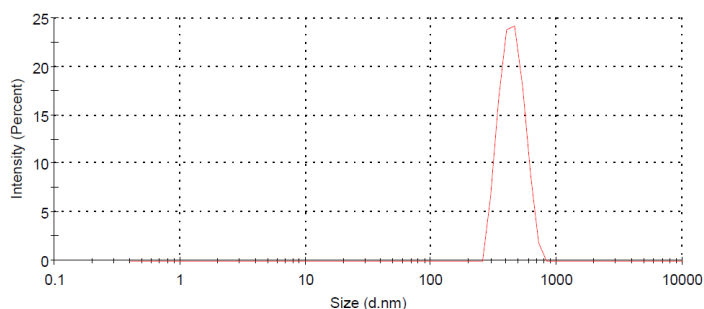
Technology for tableted FDF preparation

Previously, a tableted FDF based on sulfated arabinogalactan in the form of potassium salt with a dosage of the active component of 500 mg, had been designed. Anhydrous lactose, low-molecular polyvinylpyrrolidone and aerosil were used as adjuvants [34]. The shelf life of the tablets, obtained by direct compression with a monocomponent composition of adjuvants, was no more than two and a half years because of a high hygroscopicity of such sulfated arabinogalactan and the absence of protective coatings from the atmospheric moisture in the tablets.

Therefore, in order to increase stability and extend the shelf life of tablets derived from sulfated arabinogalactan, the composition and technology (the selection of modern combined adjuvants to improve flowability and compressibility; the selection of film moisture-protective coatings for tablets; the approbation of wide used granulation method for the directed enlargement of the particles), were experimentally optimized.



A



B

Figure 2 – Shape and size of sulfated arabinogalactan particles in the form of potassium salt

Note: A – scanning electron microscopy (200–600 nm); B – dynamic light scattering method (585.9 nm)

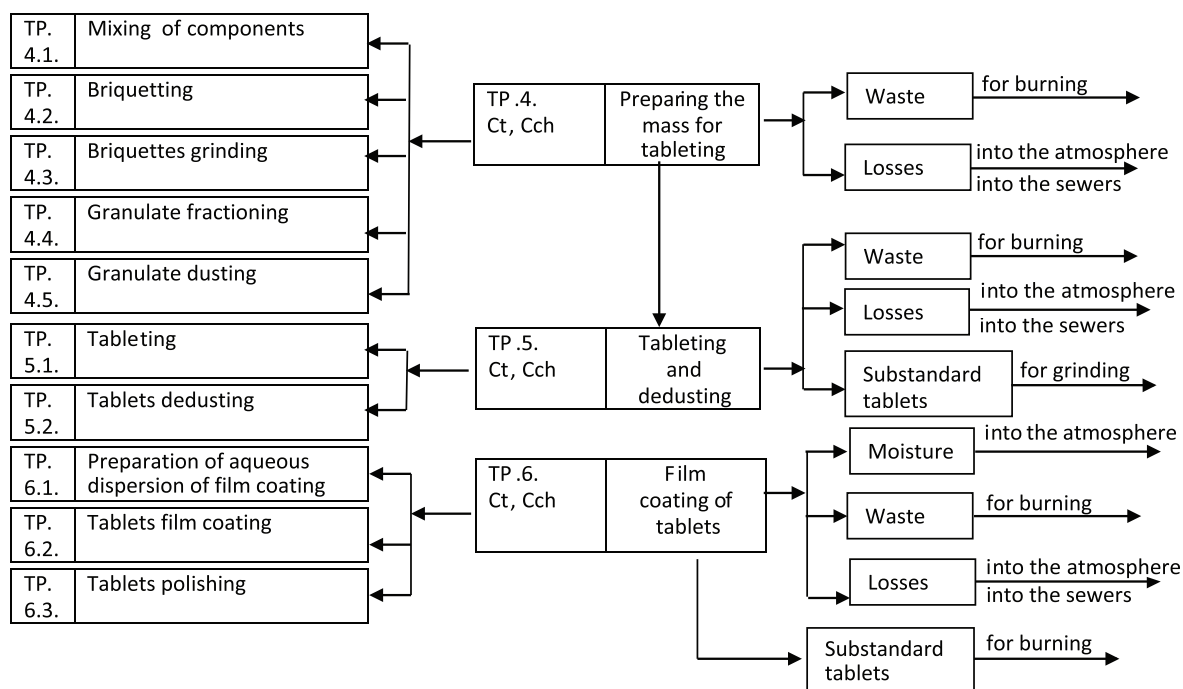


Figure 3 – Fragment of technological scheme for manufacture of "Agsular® film-coated tablets 500 mg"

Note: Ct, Cch are technological and chemical control, respectively

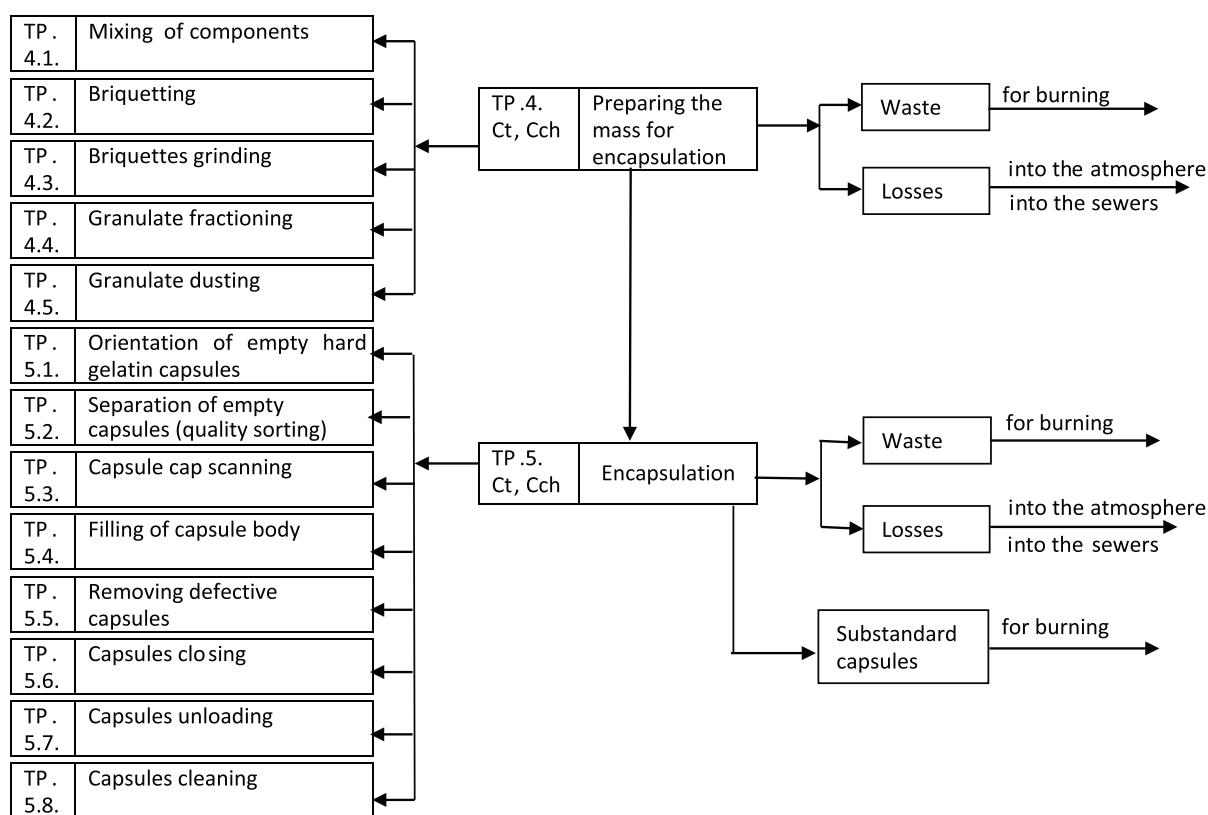


Figure 4 – Fragment of the technological scheme for the manufacture of "Agsular® capsules 500 mg"

Note: Ct, Cch are technological and chemical controls, respectively

Table 1 – Physico-chemical properties of sulfated arabinogalactan in the form of potassium salt

Average molecular weight, kDa	Solubility, kg/m ³	Average density, kg/m ³	Specific surface area, m ² /kg	Hygroscopicity, %	Found (%)			
					Calculated (%)			
					C	H	S	K
27.5	300; H ₂ O	843.17	13.88	20.07	26.63 25.39	2.26 3.23	11.01 11.48	15.55 13.99

Table 2 – Technological parameters of sulfated arabinogalactan in the form of potassium salt

Technological characteristics	Experimental data	Reference values
Granulometric composition	Fractions: < 0.25 mm 19.8%; 0.25–0.5 mm 59.5%; 0.5–1.0 mm 8.6%; 1.0–2.0 mm 10.5%; 2.0–3.0 mm 1.4%; > 3.0 mm 0.2%	Granulometric composition: more than 60% should be fractions with a particle size of 0.5–2 mm; less than 20% – fractions with a particle size of up to 0.2 mm [30].
Flowability, g/s	1.00±0.05	8.6–12 g/s – excellent; 6.6–8.5 g/s – good; 3–6.5 g/s – satisfactory; 2–3 g/s – allowable; 1–2 g/s – bad; 0.3–1 g/s – very bad [31].
The angle of the natural slope	43–45°	25–30° – very good flowability; 31–35° – good flowability; 36–45° – satisfactory degree of flowability; 46–55° – unsatisfactory degree of flowability (additional stirring or vibration is required); 56–65° – poor flowability; > 66° – very poor flowability ¹¹
Compressibility (breaking strength), N	24.50±1.14	> 70 N – good 40–70 N – medium < 40 N – bad [26].
Bulk density before compaction, g/ml	0.633±0.032	> 2.0 g/ml – very heavy; from 1.1 to 2.0 g/ml – heavy; from 0.6 to 1.1 g/ml – medium; < 0.6 g/ml – light bulk materials [31].
Bulk density after compaction, g/ml	0.843±0.042	
Hausner index	1.33	1.00–1.11 – very good compressibility; 1.12–1.18 – good compressibility; 1.19–1.25 – average compressibility; 1.26–1.34 – satisfactory compressibility; 1.35–1.45 – poor compressibility; 1.46–1.59 – very poor compressibility; > 1.60 – a very poor compressibility [32].
Carr index, %	24.91	10 – very good compressibility; 11–15 – good compressibility; 16–20 – average compressibility; 21–25 – satisfactory compressibility; 26–31 – poor compressibility; 32–37 – very poor compressibility; > 38 – a very poor compressibility [33].

¹¹ Ibid.

Table 3 – Composition and technological characteristics of tablet mixtures based on sulfated arabinogalactan in the form of potassium salt

Components, technological parameters	Tablet mixtures, wt. %			
	No. 1	No. 2	No. 3	No. 4
Sulfated arabinogalactan in the form of potassium salt	47.15	61.88	73.33	82.92
Ludipress	47.15	30.94	18.34	13.27
Aerosil	4.70	6.18	7.33	3.31
Calcium stearate	1.00	1.00	1.00	0.50
Flowability, g/s	5.5±0.2	2.6±0.1	2.0±0.1	1.5±0.1
Technological parameters of mixtures after briquetting				
Flowability, g/s	10.7±0.5	6.4±0.3	4.6±0.2	3.1±0.1
Compressibility (breaking strength), N	44.5±2.2	15.0±0.7	11.2±0.5	9.7±0.4
Bulk density before compaction, g/ml	1.349±0.067	1.270±0.063	1.215±0.061	0.497±0.025
Bulk density after compaction, g/ml	1.448±0.073	1.434±0.072	1.427±0.071	0.646±0.032
Hausner index	1.07	1.13	1.17	1.30
Carr index, %	6.84	11.44	14.86	23.07

Table 4 – Quality indicators of tableted FDF based on sulfated arabinogalactan in the form of potassium salt

Key indicators	Methods ¹²	Standards	Result
Description	Visual	Tablets, coated with white or almost white films, round, smooth, biconvex. On a cross section, the core of the tablet is from white to white with a slightly creamy shade.	Compliant
Authenticity	1. Polysaccharide fragments.	When a drop of 95% ethyl alcohol is added, the solution becomes cloudy.	Performed
	2. Reaction of metachromasia.	When a 0.005% solution of toluidine blue is added, the color of the dye solution changes from blue to lilac.	Performed
	3. Potassium ions (reaction B) (GPhM.1.2.2.0001.15)	When diluted acetic acid and sodium cobalt nitrite solution are added, a yellow crystalline precipitate is formed.	Performed
Uniformity of dosage	Weight (GPhM.1.4.2.0008.15)	The content of the substance of sulfated arabinogalactan in the form of potassium salt in coated tablets is determined according to method 2. Sample size is 10. First acceptance rate AV ≤15%.	Performed
Disintegration	Visual (GPhM.1.4.2.0013.15)	At least 16 out of 18 samples should completely disintegrate in 30 minutes; dissolution medium is purified water.	25.8 min Compliant
Dissolution	Spectrophotometric (GPhM.1.4.2.0014.15)	Release (not less than 75%) of the substance of sulfated arabinogalactan in the form of potassium salt is within 45 minutes; dissolution medium is purified water.	94.2% Compliant
Determination of auxiliaries	Gravimetric (GPhM.1.4.1.0015.15)	The content of aerosil and calcium stearate in film-coated tablets should be from 0.054 g to 0.066 g (0.06 g±10%) and not more than 11% of the average tablet weight (1.082 g) – 0.119 g.	0.059 g Compliant
Quantification	Spectrophotometric	Content of the substance of sulfated arabinogalactan in the form of potassium salt in one film-coated tablet should be from 0.475 g to 0.525 g (0.5 g±5%).	0.496 g Compliant

¹² Ibid.

Table 5 – Size of capsules for tablet mixtures based on sulfated arabinogalactan in the form of potassium salt, depending on their technological properties

Parameters	Tablet mixtures		
	No. 1	No. 2	No. 3
Average capsule mass contents, g	1.061	0.808	0.682
Acceptable deviation, %	7.5		
Flowability, g/s	10.7±0.5	6.4±0.3	4.6±0.2
Bulk density before compaction, g/ml	1.349±0.067	1.270±0.063	1.215±0.061
Range of the volume occupied by the granulate, ml	0.77–0.81	0.62–0.66	0.55–0.58
Size of hard gelatin capsules	00	0	0
Bulk density after compaction, g/ml	1.448±0.073	1.434±0.072	1.427±0.071
Volume range occupied by granulate, ml	0.71–0.75	0.55–0.58	0.47–0.49
Size of hard gelatin capsules	00	0	1

Table 6 – Quality indicators of encapsulated FDF based on sulfated arabinogalactan in the form of potassium salt

Key indicators	Methods ¹³	Standards	Results
Description	Visual	Hard gelatin capsules No. 1 or 0 or 00 with a white body and a pink lid. The content of the capsules is a compact mass from white to white-creamy.	Compliant
Authenticity	1. Polysaccharide fragments.	When a drop of 95% ethyl alcohol is added, the solution becomes cloudy.	Performed
	2. Reaction of meta-chromasia.	When a 0.005% solution of toluidine blue is added, the color of the dye solution changes from blue to lilac.	Performed
	3. Potassium ions (reaction B) (GPhM.1.2.2.0001.15)	When diluted acetic acid and sodium cobalt nitrite solution are added, a yellow crystalline precipitate is formed.	Performed
Mass uniformity	Weight (GPhM.1.4.2.0009.15)	The average weight of the contents of capsules No. 00 is from 0.981 to 1.141 g (1.061±7.5%). The average weight of the contents of capsules No. 0 is from 0.747 to 0.869 g (0.808±7.5%). The average weight of the contents of capsules No. 1 is from 0.631 to 0.733 g (0.682±7.5%). No more than two individual masses may deviate from the average mass by an amount exceeding the acceptable deviation. In this case, no individual mass should deviate from the average mass by an amount that is twice as high as the acceptable deviation.	Capsules No. 00 – 1.084 g; Capsules No. 0 – 0.798 g; Capsules No. 1 – 0.696 g. Compliant
Dosage uniformity	Weight (GPhM.1.4.2.0008.15)	The content of sulfated arabinogalactan in the form of potassium salt in capsules is determined according to method 2. The sample size is 10. The first acceptance rate AV ≤15%.	Performed
Disintegration	Visual (GPhM.1.4.2.0013.15)	At least 16 out of 18 samples should completely disintegrate in 30 minutes; the dissolution medium is purified water	Capsules No. 00 – 27.4 min; Capsules No. 0 – 26.2 min; Capsules No. 1 – 26.6 min; Compliant
Dissolution	Spectrophotometric (GPhM.1.4.2.0014.15)	The release (not less than 75%) of sulfated arabinogalactan in the form of potassium salt is within 45 minutes; the dissolution medium is purified water.	Capsules No. 00 – 91.8%; Capsules No. 0 – 90.8%; Capsules No. 1 – 91.3%. Compliant
Determination of auxiliaries	Gravimetric (GPhM.1.4.1.0015.15)	The content of aerosil and calcium stearate in capsules No. 00 should be from 0.054 g to 0.066 g (0.06 g±10%) and not more than 11% of the average weight of the capsule contents (1.061 g) – 0.117 g. The content of aerosil and calcium stearate in capsules No. 0 should be from 0.052 g to 0.064 g (0.058 g±10%) and not more than 11% of the average weight of the capsule contents (0.808 g) – 0.089 g. The content of aerosil and calcium stearate in capsules No. 1 should be from 0.051 g to 0.063 g (0.057 g±10%) and not more than 11% of the average weight of the capsule contents (0.682 g) – 0.075 g.	Capsules No. 00 – 0.058 g; Capsules No. 0 – 0.057 g; Capsules No. 1 – 0.062 g. Compliant
Quantitative determination	Spectrophotometric	The content of sulfated arabinogalactan in the form of potassium salt in one capsule should be from 0.475 g to 0.525 g (0.5 g±5%).	Capsules No. 00 – 0.501 g; Capsules No. 0 – 0.511 g; Capsules No. 1 – 0.477 g. Compliant

¹³ Ibid.

From a large assortment of modern combined adjuvants, Ludipress®, consisting of a complex of α -lactose monohydrate (93.4%), polyvinylpyrrolidone (Kollidon 30) (3.2%) and 3D polyvinylpyrrolidone (Kollidon CL) (3.4%)¹⁴, was chosen. Ludipress has the same qualitative composition of ingredients that had been used earlier to obtain tablets based on sulfated arabinogalactan in the form of potassium salt, but it is characterized by the optimal quantitative combination. That makes it possible to obtain sufficiently stable tablets under a low pressure of compression and to improve the technological properties of the active substance [35].

Since sulfated arabinogalactan in the form of potassium salt is a hygroscopic and thermolabile compound, the briquetting technique (a kind of dry granulation method) was employed to improve the flowability of the tableting mixture and prevention of its separation [36–37].

For the experiments, the model compositions of tablet mixtures were obtained, and their main technological properties were studied (Table 3).

As Table 3 shows, only tablet mixture No. 1 satisfies the technological requirements of the tableting process, because it has an excellent flowability, an average breaking strength and a very good compressibility [31, 38]. The results obtained confirm the right choice of its optimal composition and technology. Tablet mixtures No. 2 and No. 3 can be used to prepare FDFs for the peroral administration as capsules.

To protect sulfated arabinogalactan in the form of potassium salt from the effects of the atmospheric moisture, an effective film coating for tablets was selected. Hydrophobic polymers or hydrophobic polymers in combination with hydrophilic additives or hydrophilic polymers in combination with hydrophobic additives are most often used as moisture-proof coatings [39]. Such structure-forming moisture-protecting compounds as ethyl cellulose (insoluble in water, but permeable to aqueous solutions) [40] and cetyl alcohol, possessing emulsifying and stabilizing properties, were chosen as film-forming agents [41].

In modern pharmaceutical engineering, finished commercial film-forming compositions (FFCs) are widely used in the form of solutions consisting of a film-forming agent, plasticizer, colorant and solvent taken in the optimum ratio, as well as semi-products in the form of granules (powders). From the latter, a film-forming solution (dispersion) is prepared immediately prior to application using an appropriate solvent [42–45]. From all the nomenclature of FFCs containing ethyl cellulose and cetyl alcohol, Aquacoat ECD film coating was selected for the experimental studies on the protection of tablets from the atmospheric moisture; the tablets were based on

sulfated arabinogalactan in the form of potassium salt. This FFC is used as a 30% aqueous dispersion obtained immediately prior to use. The advantage of the specified HPC is the possibility of its application not only for creating a barrier coating (the application in the amount of 1–2% of the tablet weight) but also for maintaining the pH-independent mode of the release (the application in the amount of 8–15% of the tablet weight¹⁵). In addition, Aquacoat ECD is compatible with most alcohol- and propyleneglycol-soluble dyes, as well as various types of plasticizers. It promotes the formation of high-resistant, stable, easily dissolvable (in the stomach) coating, giving the tablet a pleasant appearance and effectively protecting the active substance from the atmospheric moisture [46].

The technology for the preparation of a solid pharmaceutical for a peroral administration in the form of film-coated tablets based on sulfated arabinogalactan in the form of potassium salt according to the formulation of the tablet mixture No. 1, was elaborated using Pharmag equipment and a tablet press with one CPR-6 compression station (Fig. 3).

As a result, biconvex tablets with a diameter of 12 mm of high strength (44.5 ± 2.2 N) were obtained.

Quality evaluation of the tableted FDF

The quality of the tablets obtained was evaluated according to the following parameters: description, authenticity, dosage uniformity, disintegration, dissolution, determination of auxiliaries (aerosil and calcium stearate) and quantitative determination (Table 4).

According to the studies, the developed solid dosage formulation of FDF for the oral administration in the form of film-coated tablets based on sulfated arabinogalactan in the form of potassium salt, withstands all tests and fully complies with the requirements of the GPhM.1.4.1.0015.15 “Tablets”¹⁶.

The data obtained form the basis for the development of regulatory documents and laboratory regulation for the production of “Agsular® film-coated tablets 500 mg”.

Technology for preparation of encapsulated FDF

In order to prepare FDF based on sulfated arabinogalactan in the form of potassium salt in the form of capsules, the granulate, according to the recipes of tablet mixtures No. 1–3, was placed in hard gelatin capsules of size No. 00-1, respectively (Table 5).

The elaboration of technology for the preparation of a solid pharmaceutical for the peroral administration in the form of capsules based on sulfated arabinogalactan in the form of potassium salt, was carried out using

¹⁴ Ludipress® – Enabling efficient direct tableting. Available from: <http://www.pharmaceutical.basf.com/en/Drug-Formulation/Ludipress.html>

¹⁵ Aquacoat ECD – Aqueous Dispersion Coating System. Available from: http://www.zhion.com/pharmaceutics/Aquacoat_ECD.html

¹⁶ State Pharmacopoeia of the Russian Federation XIV ed., Vol. I–IV. Available from: <http://femb.ru/pharmacopea.php>

Pharmag equipment and sets of manual machines for filling hard gelatin capsules (MC-1.2) of the appropriate size. That was due to the forced feeding of the tablet mixture into the capsule and additional pre-pressing of the material, according to the proposed technological scheme (Fig. 4).

Quality evaluation of FDF

The finished capsules were controlled according to the developed specification (Table 6). The following quality indicators were investigated: description, authenticity, mass uniformity, dosage uniformity, disintegration, dissolution, determination of auxiliaries (aerosil and calcium stearate), quantitative determination.

According to the experiments, the developed peroral solid dosage formulation of FDF in the form of cap-

sules based on sulfated arabinogalactan in the form of potassium salt withstands all tests and fully complies with the requirements of the GPhM.1.4.1.0005.15 "Capsules"¹⁷.

The data obtained form the basis for the development of regulatory documents and laboratory regulation for the production of "Agsular® capsules 500 mg".

CONCLUSION

In conclusion, the optimum compositions and technology for preparation of solid peroral dosage forms have been experimentally developed on the basis of potassium salt of sulfated arabinogalactan (capsules and coated tablets) for the prevention and treatment of blood vessels atherosclerosis. The data obtained make possible to plan a placebo-controlled clinical trial of the 1st phase.

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CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

AUTHORS' CONTRIBUTION

Yana A. Kostyuro – experimental work execution, research results processing, text writing; Konstantin V. Alekseev – concept and design of the study development, management of experimental work, text editing.

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AUTHORS

Yana A. Kostyro – Candidate of Sciences (Pharmacy), Senior Researcher of the pharmaceutical development group of the A.E. Favorsky Irkutsk Institute of Chemistry Siberian Branch of the Russian Academy of Sciences. ORCID ID: 0000-0003-2660-4796. E-mail: yanakos@iriokh.irk.ru

Konstantin V. Alekseev – Doctor of Sciences (Pharmacy), Professor, Chief Researcher of the Laboratory of finished dosage forms. ORCID ID: 0000-0002-8350-2158. E-mail: alekseev@academpharm.ru