Development of technical regulations for the capsulated probiotic manufacture

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The aim of this work was to develop a technological regulation for the production of probiotic based on lako- and bifidobacteria in the form of intestinal-soluble capsules for farm animals. Three experimental series of probiotic drug were made in the form of enteric capsules based on lactic acid bacteria. It has been established that the Bifidobacterium adolescentis No 17-316 strain and the Lactobacillus plantarum No 7-317 strain are the most adapted for the bacterial consortium. These strains have high biological activity and correspond to certain authentic characteristics. The pharmaceutical composition is proposed in the form of capsules with following ingredients: 50% of dry biomass of Lactobacillus plantarum No 7-317 and Bifidobacterium adolescentis No 17-316 strains, 5% of glucose, 5% of lactose, 9% of aerosil and 31% of starch. The content of lyophilized bacteria in one capsule is not less than 1 × 10^7 CFU of bifidobacteria/cm² and 1 × 10^7 CFU of lactobacilli/cm². A scheme of the manufacturing process of the drug in form of capsules includes the following stages: production of nutrient media and working solutions; growing cultures of lako- and bifidobacteria; freeze drying of cultures of lako- and bifidobacteria, obtaining a dry mass of lactic acid bacteria for encapsulation, encapsulation of the drug, control of the manufactured product before release, marking, packaging of capsules, transportation, storage of a drug.

Key words: lactobacilli, bifidobacteria, glucose, lactose, aerosil, starch, encapsulated drug.

Introduction

Gastrointestinal diseases in farm animals are one of the problems that have various etiologies and reduce the profitability of animal husbandry. Digestion processes and the course of many basic biochemical processes in the body are disrupted as a result of a decrease of level of the beneficial microflora (bifidobacteria and lactobacilli) in a gastrointestinal tract in animals. As a result, the general condition of the body worsens and its resistance decreases to the action of pathogenic and opportunistic microorganisms (Hadzevych et al., 2019; Kolchyk et al., 2020). Probiotic drugs are the main means for prevention and treatment of the gastrointestinal tract diseases caused by dysbiosis. The use of these drugs makes it possible to improve and restore the state of the intestinal microflora and mucous membranes of the animal body in some cases. It leads to a general improvement state of health and prevents the development of a number of chronic diseases (Oihland & Macnaughton, 2010; Floch et al., 2011; Piquet et al., 2019; Kasianenko et al., 2020). The sphere of production and use of probiotics based on strains of lactobacilli and bifidobacteria has expanded today (Gill & Prasad, 2008; Kianifar et al., 2014; Guvinska et al., 2018).

There are several points that are important when selecting a probiotic for the genetic stability, survival and technical properties of the strain. Although each bacterial strain is unique. Appropriate ingredients, nutritional matrices and manufacturing processes need to be selected because matrices can affect the viability of the strain in the product and in the intestine (Forstens et al., 2011). Probiotic cultures are exposed to many aggressive influences when passing through the digestive tract. It leads to a decrease in their activity and partial or complete death (Dimidi et al., 2017). The main risk factors for probiotic microorganisms are their long-term location in the acidic environment of a stomach, the influence of antimicrobial components contained in foods, the effect of bile acids, and the effect of oxygen (Terpou et al., 2019). Encapsulation of probiotic cultures is one of the ways to preserve their activity and viability in aggressive conditions of the gastrointestinal tract. The capsules provide cell protection and nutrient delivery to the gastrointestinal tract. The capsule protects living bacteria from various factors such as...
The range of probiotic drugs for animals is rather limited on the Ukrainian market due to the lack of effective strains of lactic acid bacteria and appropriate technologies. Medicines of this pharmacotherapeutic group are presented in the form of such dosage forms as powders, drops, tablets and capsules on the market. Foreign manufacturers prefer the production of probiotics in the form of capsules (56%) when comparing the dosage forms of probiotic drugs of domestic and foreign manufacture. Modern intestinal-soluble dosage forms of combined probiotics are not present among domestic probiotic drugs in the form of capsules for prophylactic and therapeutic use. Thus, research in this direction is timely relevant (Di Cerbo & Palmieri, 2015). The improvement and development of new drugs based on innovative compounds and living cultures of microorganisms is one of the urgent tasks of modern biotechnology (Zykova et al., 2018; Fenster et al., 2019; Orobchenko et al., 2020).

The aim of this work was to develop the technological regulations for the production of lactic- and bifidobacteria probiotics in capsules form for the farm animals.

Materials and methods
The development of technological regulations for the manufacture of probiotics based on lactic- and bifidobacteria in the form of capsules was carried out in the Laboratory of Veterinary Sanitation and Parasitology of the National Scientific Center “Institute of Experimental and Clinical Veterinary Medicine” (Kharkiv). The development of a probiotic drug was carried out on the basis of microorganisms Lactobacillus plantarum No 7.317 and Bifidobacterium adolescentis No 17.316. Glucose, lactose, aeosil, starch and intestinal soluble capsules were used in various ratios as constituents of the probiotic. Cultivation of lactobacilli and bifidobacteria was carried out on MRS agar and Blaurock nutrient medium as well as on a skim milk at 37 °C for 24-72 hours (Süle et al., 2014; Hayek et al., 2019; Paliy et al., 2020c).

A lyophilic drying of lactic acid bacteria was carried out on the “LZ-4527” installation according to the following technological regime: the temperature increased from minus 72 °C to 26 °C. A drying time was 26-28 hours (Paliy et al., 2020b). The resulting initial culture of probiotic microorganisms was mixed with glucose (5-7%), lactose (5-7%), aeosil 200 (8-9%), starch (residue). The number of lyophilized bacteria in one capsule was at least 10⁷ colony forming units (CFU) of each probiotic culture. Hard gelatin enteric capsules of size “2” were selected as the capsule mass. A probiotic preparation was tested according to the following criteria: determination of the appearance, microbiological purity (bacteriological control and the absence of extraneous microflora), harmlessness, specific activity (the number of live bacteria in one dose of the preparation) (Chen et al., 2017; Drago et al., 2020; Gujvinska & Paliy, 2018a).

Determination of appearance and color was carried out visually. Bacterial control was carried out in accordance with DSTU 4483. The number of living microbial cells in the preparation was determined by the method of serial dilutions of the resulting suspension in physiological solution followed by inoculation of bacterial cultures diluted to 10⁶ in a dose of 0.1 cm³ on MRS agar and Blaurock nutrient medium (Davis, 2014). In order to determine the harmlessness of the probiotic, it was dissolved by 0.9% sodium chloride solution at the rate of 0.5 ml per dose and administered perorally to laboratory animals (n=10) into the stomach using a special attachment for syringes with a volume of 2 ml. Ouabain white mice receiving 18-20 g were used as laboratory animals. The animals were observed for 5 days (Donohue & Salminen, 1996). The biological properties of the drug were studied in the course of study (determination of the acid formation activity of lactobacilli and bifidobacteria and their biochemical activity) (Chen et al., 2017; Gujvinska & Paliy, 2018b).

Determination of the activity of acid formation of lactobacilli was carried out by titrimetric method. The contents of the capsule were dissolved in 25.0 ml of Blaurock nutrient medium (at the rate of 10 ml per 1 dose) and placed in a thermostat at a temperature of 38.0±0.5 °C with stirring every 10 minutes until complete dissolution in order to determine the acid formation activity of bifidobacteria in one capsule. The culture of bacteria with a volume of 2.5 ml was transferred into wide test tubes (2 cm diameter and 20 cm height) containing 25.0 ml of Blaurock nutrient medium (at the rate of 1 ml of culture per 10 ml of medium). The tubes were kept at a temperature of 38.0±0.5 °C for 72 hours. After that, the acidity was determined in each test tube (in two parallel tubes). Each sample (10 ml of microbial suspension) was titrated with a sodium hydroxide solution at a concentration of 0.1 M until a stable pale pink color appeared. The pH value was controlled by potentiometer. The titration was carried out to pH 8.5.

The acidity was expressed in Turner degrees (°T) and calculated by the following formula:

\[ T = A \times K \times 10 \]

where A – the amount of 0.1 M sodium hydroxide solution, which was used for titration, ml; K – correction to the titer of 0.1 M sodium hydroxide solution that was used; 10 – the degree of dilution of the microbial suspension. Inoculations were made into test tubes with skim milk (a dose was 0.2 cm³ per 5 cm³ of milk) and the time of milk clotting was measured to determine a biochemical activity of the diluted probiotic (Gujvinska & Paliy, 2018a). Statistical processing of the results was carried out by Excel and Statistica v. 10 software. Differences between the values were considered significant at p<0.05.

Results and discussion
To date, a large number of dietary supplements and medicines have been created in different countries. These means are based on cultures of normal human or animal microflora (Shi et al., 2016; da Silva et al., 2019). Typically, different strains of bifidobacteria and lactobacilli, non-pathogenic strains of Escherichia coli and enterococci are used (Rossi et al., 2013). Lactobacilli and bifidobacteria are the best known microorganisms that are used as the basis for probiotic biologics (Forsssten et al., 2011; Paliy et al., 2020c). Lactic and acetic acids are the main end products of their metabolism (Tejero-Sarihena et al., 2012). The following bacterial strains were cultivated on a nutrient medium in order to select probiotic strains for creation a
bacterial consortium: *L. plantarum* 19, *L. plantarum* 7-317, *B. longum* 23, *B. adolescens* 17-316. These strains are cultivated separately and in the ratio 1:1. The amount of inoculum of one bacterial strain in one dose was at least 10^7 CFU/cm^3 (Table 1).

### Table 1. Characteristics of the biological activity of various consortia of bacteria (n=5, M±m)

| Number of sample | Lactobacillus spp., 10^7 CFU/cm^3 | Bifidobacterium spp., 10^7 CFU/cm^3 | Acid formation activity, °T | Number of living bacteria, CFU/cm^3 |
|------------------|-----------------------------------|-------------------------------------|-----------------------------|-----------------------------------|
| 1                | *L. plantarum* 7-317               | *B. adolescens* 17-316              | 280±17                      | (6.2±0.18)×10^9                 |
| 2                | *L. plantarum* 19                  | *B. adolescens* 17-316              | 220±10                      | (3.7±0.18)×10^9                 |
| 3                | *L. plantarum* 7-317               | *B. longum* 23                     | 240±10                      | (4.2±0.17)×10^9                 |
| 4                | *L. plantarum* 19                  | *B. longum* 23                     | 215±15                      | (4.9±0.15)×10^9                 |
| 5                | *L. plantarum* 19                  | -                                   | 180±8                       | (4.4±0.13)×10^7                 |
| 6                | *L. plantarum* 7-317               | -                                   | 260±5                       | (4.2±0.13)×10^8                 |
| 7                | -                                  | *B. adolescens* 17-316              | 220±10                      | (3.4±0.13)×10^9                 |
| 8                | -                                  | *B. longum* 23                     | 200±8                       | (3.5±0.11)×10^7                 |

*p<0.05

A data presented in Table 1 shows that the acid formation activity was the best and amounted to 280±17°T, the number of living bacteria was 6.2±0.18 × 10^9 CFU/cm^3 during co-cultivation of *L. plantarum* 7-317 and *B. adolescens* 17-316 cultures. The acid formation activity was 260±5°T and the number of living bacteria was 4.2±0.13 × 10^8 CFU/cm^3 with separate cultivation of *L. plantarum* 7-317. It should be noted that the rate of acid formation activity was also low and amounted to 220±10°T, and the number of living bacteria was 3.4±0.13 × 10^7 CFU/cm^3 during separate cultivation of the *B. adolescens* 17-316 strain. Thus, the strains for experimental studies on the creation of a bacterial consortium were determined on the basis of the maximum values of the main growth parameters by the method of co-cultivation of the *Bifidobacterium adolescens* 17-316 and the *Lactobacillus plantarum* 7-317 strains.

The cells of the *Lactobacillus plantarum* No 7-317 strain are gram-positive rods and belong to the species *Lactobacillus plantarum*, the genus *Lactobacillus*, the family *Lactobacillaceae*. Lactobacillus grown on MRS-2 nutrient medium have a brushlike growth in middle and lower parts of the test tube. The colonies have a diameter of 2-5 mm, convex, with entire edges, opaque, non-pigmented on agar media. The cells have a size of 0.5-1.2 × 1.0-10.0 μm and rod-shaped in smears. The sticks are long, kokkoid and arranged in short chains. The culture exhibits fermentation-type metabolism, does not reduce nitrate and does not liquefy gelatin. It is catalase-negative and does not contain cytochromes.

The cells of *Bifidobacterium adolescens* No 17-316 strain belong to the *Bifidobacterium bifidum* species, the genus *Bifidobacterium*. Gram-positive rods are about 0.5-1.3 × 1.5-8 μm in size, variable in shape and location, usually curved, clavate, and often branched at the ends and motionless. Cells were stained unevenly after 48 hours of cultivation. They form creamy white colonies, convex, round, with even edges, 1-2 mm in diameter and pasty consistency on the surface of a solid nutrient medium. The studied strains form colonies on a semi-liquid medium in the form of “comets” and “nails”. A bottom growth in a high column of the nutrient medium is observed in a liquid medium. A uniform growth over the entire volume of the medium is observed under anaerobic conditions. The strains do not have catalase and nitrate reductase activity and do not form gas from glucose. A complex of physical and physico-chemical factors (pH and temperature) is important for productive cultivation and maximal biomass accumulation (Broeckx et al., 2016). Optimal conditions for the growth and accumulation of lactic acid bacteria biomass (pH, cultivation temperature) are given in Table 2.

### Table 2. Optimal growth conditions for bifidobacteria and lactobacteria with separate and co-cultivation

| Value | Bifidobacterium adolescens No17-316 | Lactobacillus plantarum No7-317 | Pooled bacterial culture |
|-------|-------------------------------------|---------------------------------|-------------------------|
| pH    | 6.5±0.1                             | 7.0±0.1                         | 7.0±0.1                 |
| Temperature, °C | 38±0.5                 | 37±0.5                         | 37±0.5                   |

We have experimentally established that the proposed cultivation regime allows the simultaneous cultivation of bifidobacteria and lactobacilli in the same volume while preserving the main morphological and biological parameters. The general tendency to expand the field of application of probiotic preparations in veterinary medicine necessitates the creation and use of new dosage forms. Thus, the action of new dosage forms is aimed at protecting bacteria from the destructive effects of the acidic environment of the stomach and bile acids, the ability to simultaneously introduce several prebiotic components. These opportunities are provided by the use of the drug in the form of intestinal-soluble capsules (Sakandar et al., 2018). It was proved that foreign manufacturers give preference (56%) to the production of probiotics or symbiotics in the form of capsules when comparing dosage forms of domestic and foreign probiotic drugs (Candela et al., 2010; Muhrdina et al., 2018). The production of capsules implies the improvement of technological measures used to stabilize cultures of bifidobacteria and lactobacilli to obtain dry biomass with improved indicators of hygroscopicity and fluidity of the material for organizing production in accordance with the requirements of regulatory documents (Šipailienė & Petraitytė, 2018). A number of excipients are used for these purposes (Fasoli et al., 2003; Vijaya Kumar et al., 2015; Ullah et al., 2019).

The filler must meet the following requirements: uniformity of the capsule filling material, a sufficient level of fluidity to ensure the technological process of encapsulation and the bulk density of the filler corresponding to the size of the capsule for filling when developing the formulation of the preparation in the form of capsules (Gbassi & Vandamme, 2012). Anhydrous lactose or lactose monohydrate, maltodextrin and fructooligosaccharides are used as filler in the production of encapsulated probiotic preparations by foreign manufacturers. Combined forms of lactose with starch, cellulose derivatives are of practical importance. The introduction of microcrystalline cellulose derivatives into the capsule composition improves the stability and
Bacterial biomass is highly hygroscopic due to the content of gelatin and sucrose in the cryoprotectant. The content of lyophilized bacteria is at least 5% of dry biomass of the powder mass (Fuentes-Zaragoza et al., 2011; Marcial-Coba et al., 2019). We selected lactose with a particle size of 75 μm (has a low moisture content) from the group of fillers. The amount of lactose was 3-5% as a filler per one capsule. A small amount of lactose is due to the presence of prebiotic components in the drug and use of cryoprotectant (Paliy et al., 2020b).

Calcium stearate is most often used in an amount of 1-3% as a lubricant to reduce friction between particles according to the literature data (Ephrem et al., 2018). An antifriction substance aerosil 200 (silicon dioxide) was introduced into the capsule mixture in the amount of 8-9% to improve the technological parameters of the lyophilized bacterial culture due to its low bulk density and fluidity, tendency to sticking and extreme hygroscopicity. It has been shown that aerosil prevents the adhesion of the capsule mixture to the walls of the dispenser used for the manufacture of capsules. Aerosil is adsorbed on the surface of biomass particles due to hydrogen bonds and increases the fluidity of the capsule mixture. A brand of “Aerosil 200” was selected for use in hydrophilic mixtures of medicinal substances based on the experimentally proven advantages and data described in the literature (De Souza et al., 2000; Li et al., 2015). The effect of lubricants on bacterial culture was determined based on the level of an indicator of the activity of acidification of bacteria (Table 3).

Table 3. Activity of acid formation of bacteria in samples of capsule mixtures (n=3, M±m)

| Number of sample | Name of leavening agent | Volume of leavening agent, % | Value of the acid formation activity indicator, °Т |
|------------------|-------------------------|-------------------------------|---------------------------------------------|
| 1                | Aerosil 200             | 7                             | 315±7                                       |
| 2                | Aerosil 200             | 8                             | 330±8                                       |
| 3                | Aerosil 200             | 9                             | 335±12                                      |
| 4                | Calcium stearate        | 2                             | 220±6                                       |
| 5                | Substance without excipients | –                          | 310±14                                      |

As can be seen from Table 3, the use of calcium stearate as a lubricant has a negative effect on bacteria and causes a significant decrease in their level of acid formation activity to a value of 220°Т. The indicator of the acid formation activity of bacteria without the use of excipients is 310±14°Т and slightly differs from the samples with aerosil. The use of aerosil has the best effect since the rate of acid formation activity is quite high and has a value of 315-335°Т. The amount of aerosil in the range of 7-9% does not cause changes in the activity of bacterial strains. However, it affects the appearance and fluidity of the capsule mass. Also, glucose was used as a carbohydrate source for the manufacture of an encapsulated probiotic in the amount from 5% to 7%. Hard gelatin intestinal soluble capsules No. 2 with white opaque lid and white opaque body were selected for the capsule mass. A mass of the contents of one capsule was 0.36±0.03 g. The dimensions of the capsule were as follows: wall thickness about 0.10±0.01 mm in a top with diameter 6.20 mm; wall thickness about 0.10±0.01 mm in a bottom with diameter 6.00-6.14 mm. A capsule length was 17.0-17.8 mm. A compound of the pharmaceutical composition was proposed in the form of capsules. There are 50-60% of dry biomass of Lactobacillus plantarum No 7-317 and Bifidobacterium adolescentis No 17-316, 5-7% of glucose, 5-7% of lactose, 8-9% of aerosil and starch as a residue. A content of the lyophilized bacteria is not less than 10^7 CFU in one capsule. Three series of probiotic drug were produced (Table 4).

Table 4. Composition of the capsule mass of test samples

| Name of the component | Number of components, % |
|-----------------------|-------------------------|
| Sample No. 1          | Sample No. 2            |
| Bacterial biomass     | 50±3                    | 55±3                     | 60±3                     |
| Glucose               | 5±1.2                   | 6±1.3                    | 7±1.3                    |
| Lactose               | 5±1.2                   | 4±1.1                    | 3±1.2                    |
| Aerosil 200           | 9±1.2                   | 8±1.3                    | 9±1.5                    |
| Starch                | the rest                | the rest                 | the rest                 |

A technology for the production of an encapsulated form of a probiotic preparation was developed based on the results of the conducted studies. This technology includes the following steps: production of nutrient media and working solutions; growing cultures of lacto- and bifidobacteria; freeze drying of cultures of lacto- and bifidobacteria; obtaining mass for encapsulation; drug encapsulation; control of the finished product before release; labeling, packaging of capsules, transportation, storage of the probiotic. The list of physiological functions of beneficial bacteria has been fairly well reviewed in the literature. The functions that bacteria perform in the human body are commonly used to create new types of probiotics. Strains in the composition of biological products should have a high growth rate, acid formation activity for successful use in the technological process (Tuomola et al., 2001). Analysis of a technology for the production of bacterial preparations showed that an improvement of the initial basic stages of production in a context of creating the most productive conditions for the accumulation of biomass (optimization of the composition of nutrient medium) is an important and promising direction (Paliy et al., 2020a). We have proposed an innovative compound of a pharmaceutical composition in the form of capsules based on the obtained results (Table 5).

The content of lyophilized bacteria is at least 1×10^7 CFU of bifidobacteria/cm³ and 1×10^7 CFU of lactobacilli/cm³ in one capsule. Bacterial biomass is highly hygroscopic due to the content of gelatin and sucrose in the cryoprotectant. The control of the technological process is a prerequisite for the production of the drug. The bacterial synbiotic consortium for oral administration must be controlled according to the following indicators: species; harmlessness; contamination with bacterial and fungal microflora; harmlessness; specific activity (the number of living bacteria in one dose, the activity of acidification of bacteria) (Table 6).

Table 5. Composition of an innovative capsule mixture
Biomass of bacteria strains:

| Bifidobacterium adolescentis No17-316 |
|--------------------------------------|
| Lactobacillus plantarum No7-317 |

| Composition, % |
|----------------|
| 50.0 |

| Mass of components, g |
|-----------------------|
| 0.180 |

| Lactose |
|---------|
| 0.018 |

| Glucose |
|---------|
| 0.018 |

| Aerosil |
|---------|
| 0.032 |

| Starch |
|--------|
| 0.112 |

| Mass of capsule, g |
|--------------------|
| 0.36 |

**Table 6. The results of tests of encapsulated probiotic**

| The name of indicators | Requirements | Results of the test |
|------------------------|--------------|---------------------|
| Appearance             | Cylindrical hard gelatin intestinal soluble capsules with hemispherical ends. The body and lid are white, size No. 2. The contents of the capsule are cream-colored powder. | Cylindrical hard gelatin intestinal soluble capsules with hemispherical ends. The body and lid are white, size No. 2. The contents of the capsule are cream-colored powder. |
| Contamination with bacterial and fungal microflora | It should not be contaminated with bacterial and fungal microflora. | Not contaminated with bacterial and fungal microflora. |
| Biochemical activity | Must coagulate skimmed milk in test tubes or bottles within 48-72 hours. Incubation at 37.0±0.5°C | Coagulates skim milk in test tubes within 48 hours. Incubation at a temperature of 3.07±0.5°C |
| Harmlessness | Ten white mice weighing 18-20 g should remain alive and healthy for 5 days after ingestion of a diluted probiotic at a dose of 0.5 cm³ | Ten white mice weighing 18-20 g remained alive and healthy for 5 days after ingestion of a diluted probiotic at a dose of 0.5 cm³ |
| The number of microbial cells in 1 cm³ of probiotic | lactobacteria ≥ 10⁶ | lactobacteria ≥ 10⁶ |
| | bifidobacteria ≥ 10⁶ | bifidobacteria ≥ 10⁶ |

Capsules are packed in pieces of 10 in a blister strip made of polyvinyl chloride film, which is thermally sealed. The capsules are stored in a dry place protected from direct light at a temperature of 2-8 °C (Fig. 1).

**Fig. 1. Capsulated probiotic for farm animals**

The storage conditions of the finished probiotic product are a key step in its future efficacy (Bakr, 2015). Conventional means such as antibiotics, disinfectants and physical methods are commonly used as a germ control strategy. However, many countries have adopted laws and regulations restricting the widespread use of these means due to their emergence of sustainability, low efficiency, high cost, and harmful effects on human health, animal and environment. An environmentally friendly, cost-effective alternative and innovative scientific approach are needed to overcome these challenges (Hossain et al., 2017). The development of next-generation probiotics for the recovery of macroorganism normal flora and eliminate potential pathogenic microorganisms from the intestine is an urgent task of modern biotechnology (Pamer, 2016) along with the development of nonspecific measures for prevention and control of various animal pathologies (Paliy et al., 2020d). Probiotics have a great chance of replacing antibiotics in animal husbandry. However, it is necessary to strictly adhere to the established regulations for their application (Alayande et al., 2020; Sabo et al., 2020). Probiotics have gained widespread attention in recent decades. The use of probiotic drugs is promising in health care and animal husbandry (D’Aimmo et al., 2012; Zhou et al., 2020).

**Conclusions**

The most suitable strains for a bacterial consortium of microorganisms have been determined. These are Bifidobacterium adolescentis No 17-316 and Lactobacillus plantarum No 7-317 strains, that have high indicators of biological activity and correspond to certain authentic characteristics.

A composition of the pharmaceutical ingredients was proposed in the form of capsules. There were 50-60% of dry biomass of Lactobacillus plantarum No 7-317 and Bifidobacterium adolescentis No 17-316, 5-7% of glucose, 5-7% of lactose, 8-9% of aerosil.
and starch as a residue. The content of lyophilized bacteria is not less than 1 × 10^10 CFU of bifidobacteria/cm³ and 1 × 10^14 CFU of lactobacilli/cm³ in one capsule.

The technology has been developed for the manufacture of encapsulated probiotic drug. It includes the following steps: production of nutrient media and working solutions; growing cultures of lacto- and bifidobacteria; freeze-drying of cultures of lacto- and bifidobacteria; obtaining a mass for encapsulation; encapsulation of the drug; control of the finished drug before release; labeling, packaging of capsules, transportation, storage of probiotic drug.

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