DEVELOPMENT OF A THERAPEUTIC AGENT WITH VEGETABLE EXTRACT IN THE FORM OF TABLETS FOR GASTROENTEROLOGY

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Introduction. For a long time there has been a progressive increase in the incidence of inflammatory diseases of the upper gastrointestinal tract (GIT). The main nosologies that form a prevalence of about 40% include gastritis, duodenitis and peptic ulcer disease. The treatment of gastrointestinal diseases is complicated by the resistance of microorganisms to most antibacterial drugs that are part of traditional treatment regimens prescribed to gastroenterological patients [1].

This justifies the expediency of searching for promising objects, in particular, among medicinal plant raw materials for obtaining extracts and creating drugs based on them, further implementation, which will expand the range of agents for pharmacotherapy.

Based on previous studies, we have substantiated the choice of dry extract of *Sanguisorba officinalis* roots (DESOR) as the object of study and developed the technology of obtaining the DESOR [2, 3].

Screening studies were used to assess the pharmacological and microbiological effects of DESOR. Pharmacological studies performed on a model of subchronic erosive-hemorrhagic lesions of the gastric mucosa of rats caused by acetylsalicylic acid showed gastroprotective effect of the obtained plant object. Microbiological studies performed by the method of diffusion into agar in the modification of «wells» using test strains of microorganisms (*S. aureus* ATCC 25923, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *B. subtilis* ATCC 6633, *P. vulgaris* ATCC 4636, *C. albicans* ATCC 885-653) revealed sensitivity of all studied test strains to the object of study, in particular the greatest sensitivity to test strains of *S. aureus* and *B. subtilis*, as evidenced by the largest diameters of the zones of growth retardation of these microorganisms (24.17 ± 0.31 mm and 24.33 ± 0.33 mm, respectively) [2, 4].

When developing new drugs, scientists pay special attention to the choice of dosage form, as according to the biopharmaceutical concept, its choice depends on the bioavailability of drugs. In the domestic market there are drugs of plant origin for use in gastroenterology in various dosage forms (tablets, capsules, granules, drops, liquid extracts, tinctures, oils, packed medicinal plant raw material, suppositories) [5].

We studied the consumer preferences for drugs used in diseases of the gastrointestinal tract, according to pharmacy experts, conducted by questionnaire. According to the results of processing the questionnaires, the commitment of consumers to herbal medicines was determined, and the criteria for choosing drugs implied that the most popular were drugs in the form of tablets.

Thus, it is timely to create a new drug in the form of tablets for gastroenterology, which contains DESOR and has antimicrobial action.

Materials and methods. Objects of the study included DESOR, which is a dark brown powder with a specific odor and bitter taste, is hygroscopic, weight loss during drying does not exceed 5%; excipients: fillers based on sugars and microcrystalline cellulose, disintegrants, glidants and lubricants that meet the requirements of the State Pharmacopoeia of Ukraine (SPU), the European Pharmacopoeia, regulatory and technical documentation and are approved for medical use.

Determination of pharmaco-technological properties, namely: homogeneity of tablet weight, tablet abrasion, tablet resistance to crushing, tablet disintegration time, average tablet weight were investigated according to the methods given by the SPU [6]. The appearance of the tablets was determined visually in daylight, by observing them on a white background.

Studies of the antimicrobial activity of Gastro-San tablets were performed at of the Biochemistry and Biotechnology Laboratory of the State Institution «Mechnikov Institute of Microbiology and Immunology of NAMS of Ukraine» under the direction of Candidate of Biological Sciences Osolodchenko T. P., by the method of double serial dilutions in nutrient broth. The concept study involved 1000 μg / ml followed by dilutions of 500; 250; 125; 62.5; 31.25 μg / ml. The microbial load of the test microorganism was 5×10^5 CFU / ml. After incubation for 48, 72 hours for *Candida spp*. cultures, culture tubes were examined in radiant light to determine the presence of microorganism growth.

MIC was set at the lowest concentration of the test substance, which inhibited the visible growth of the culture. MMC was determined by dosing inoculations on a solid nutrient medium (Mueller-Hinton agar) of culture fluid from all tubes in which no growth of the microorganism was observed. MMC was considered to be the lowest concentration, which caused death of at least 99.9% of bacteria. Additionally, the study involved control of culture growth in the medium without test substances in the solvent, control of the purity of the suspension of the microorganism (by seeding on non-selective media) and sterility of the medium.

Statistical processing of the obtained results was performed using Excel software.

Results and discussion. The optimal composition of the drug was developed under the conditional name Gastro-San, containing DESOR at a dose of 40 mg per 1 tablet [7]. The choice of excipients for the development of a new drug in tablet form involved employment of one of the methods of mathematical planning of the experiment, namely hyper-Greek-Latin square, taking into account the pharmaco-technological parameters of both DESOR and powder masses with plant extract, which allowed to produce the drug by direct compression [7-9]. According to the results of the study, the following excipients were selected to be included in the tablets: compress sugar, prosolv 90, croscarmellose sodium, neuselin US 2, calcium stearate.

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The figure shows the step-by-step technology of obtaining Gastro-San tablets by direct compression.

Stage 1. Preparation of raw products and materials. The necessary components were weighed and sieved (DESOR, prosolv 90, compress sugar, croscarmellose sodium, neuselin US 2, calcium stearate). In the process of preparation, the availability of analytical sheets and permits of the quality control department, packaging materials, printed materials, sieve number, weight of raw materials were controlled. After sieving and weighing, containers with the prepared components were closed with lids, labeled and transferred to the next stages.

Stage 2. Obtaining a mass for tableting. Weighed and sieved raw materials were loaded into a V-shaped mixer and mixed. The finished mass for tableting was unloaded and weighed. During mixing, the compliance with the formulation of the weight of the loaded ingredients, mixing time, quality of the intermediate product according to the specification and the amount of mass for tableting were controlled.

Stage 3. Tableting and dedusting. The tableting operation was performed on a rotary tablet press. The following parameters of the tablet press were adjusted: average weight, geometric parameters; the first tablets obtained were checked by the rate of disintegration. In the process of tableting, the tablets were dedusted and inspected for metal inclusions. The finished tablets were unloaded by gravity into a container, closed with lids and identified by labels, weighed. In the tableting process, the quality control department's permission to use the tableting mass, geometrical parameters, basic pressure, filling depth, rotor speed, appearance and average weight of tablets, disintegration, quality of the intermediate product according to the specification, yield were monitored.

Stage 4. Pre-packing of tablets. Pre-packing of tablets was carried out on an automatic blister packing machine of 10 pieces in a blister. The process parameters were set in accordance with the characteristics of the materials for the primary packing, the batch number and expiration date were marked. Tablets in primary packaging were transferred to the next stage. Availability of permission of the quality control department for the use of tablets, labeling, batch number, expiration date, appearance of blisters, bonding quality and yield were controlled.

Stage 5. Labeling and packaging. Marking of packs was carried out using a marking machine, applying the expiration date and batch number. Labeling, batch number, expiration date, appearance, completeness of packaging and yield were controlled.

Stage 6. Quarantine storage of finished products. The finished products were stored in a quarantine storage room, identified by the «Quarantine» label of the quality control department at a temperature not exceeding 25^0C.

The product obtained by direct compression was a gray tablet with brown spots, a flat surface and a bevel. The pharmaco-technological properties of the obtained tablets were assessed, the results are presented in Table 1. Determination of the quality of the obtained tablets under the conditional name «Gastro-San» was carried out based on the general article of SPU «Tablets» and regulations.

The study showed that the quality indicators of Gastro-San tablets met the requirements of SPU.

The next step in the development of tablets for gastroenterological practice was to study their antimicrobial activity. Table 2 shows the results of the antimicrobial action of Gastro-San tablets against microorganisms that can cause gastrointestinal diseases.

The study of antimicrobial activity was performed by the method of double serial dilutions in nutrient broth. According to the results of the study, the drug Gastro-San has a moderate antimicrobial action against reference strains of gram-positive, gram-negative microorganisms, *Candida* fungi and clinical isolates of microorganisms. Screening for gram-positive test strains of *S. aureus* ATCC 25923 and *S. aureus 57* showed that the inhibitory effect was 125 μg / ml, and ATCC 6633 - 250 μg / ml for *B. subtilis*.

The study identified that the MIC for test strains of gram-negative microorganisms (*P. vulgaris* ATCC 4636, *E. coli* ATCC 25922) was at a concentration of 250 μg / ml.

In relation to clinical isolates, the MIC of *E. coli 23, K. pneumonia 13, P. vulgaris 18, C. freundii 39, E. cloacae 54, S. enteritidis 1, S. typhimurium 2, S. flexneri 3* was 250 μg / ml, in relation *to E. coli 14 (hemolytic)* and *P. mirabilis 33* antimicrobial activity was determined at the level of 500 μg / ml. The antifungal effect on the test strain of *C. albicans* ATCC 885-653 comprised 500 μg / ml.

The conducted microbiological study has revealed that the proposed drug in the form of tablets based on DESOR has antimicrobial action.

Conclusions

The timeliness of the development of a drug with antimicrobial action in the form of tablets for the treatment of diseases of the gastrointestinal tract has been proven.

The technology of obtaining Gastro-San tablets by direct compression method is given. The study of pharmaco-technological indicators of the developed tablets with DESOR determined their compliance with the requirements of SPU.

The antimicrobial action of the developed drug Gastro-San has been established, which opens prospects for its introduction into gastroenterology for the implementation of complex therapy of gastrointestinal diseases as an antimicrobial drug.

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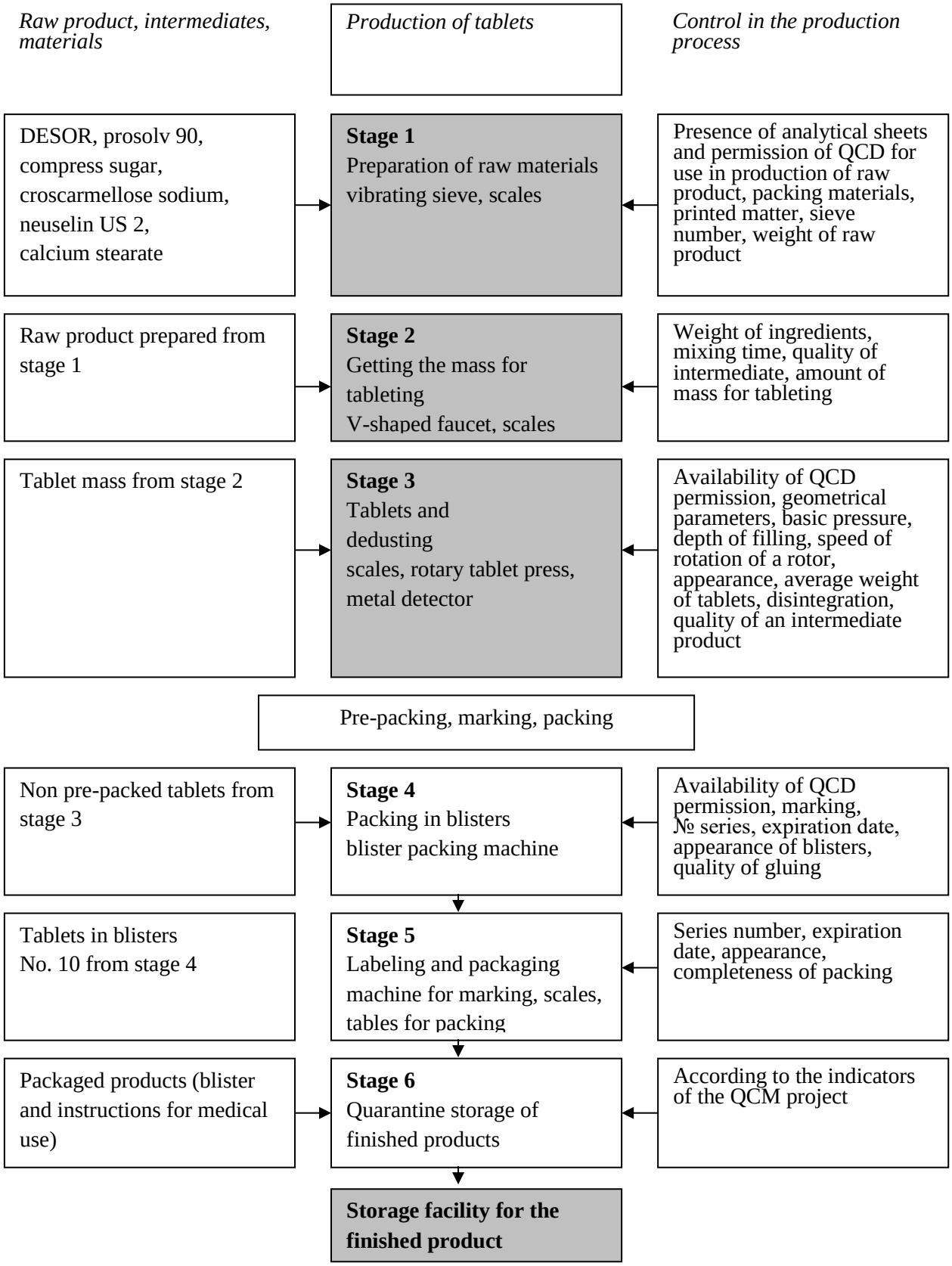

Fig. The composition of the finished product

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Table 1. Study of pharmaco-technological properties of Gastro-San tablets

Pharmaco-technological parameters	Measuring unit	Research results
Filling of a matrix	Points	5
Homogeneity of tablet weight	%	1.74±0.09
Abrasion of tablets	%	0.27±0.02
Resistance of tablets to crushing	H	152.90±1.35
Disintegration time of tablets	min	10.19±0.08
The average weight of tablets	h	0.121±0.002

Note: n = 6, P = 95 %

Table 2. Determination of antimicrobial activity of Gastro-San tablets

Archival and clinical strains of microorganisms	Antimicrobial action of Gastro-San, μg / ml	
	MIC	MMC
S. aureus ATCC 25923	125	250
E. coli ATCC 25922	250	500
P. aeruginosa ATCC 27853	500	500
B. subtilis ATCC 6633	250	250
P. vulgaris ATCC 4636	250	500
C. albicans ATCC 885-653	500	500
S. aureus 57	125	250
E. coli 23	250	500
K. pneumonia 13	250	500
P. vulgaris 18	250	500
C. freundii 39	250	500
E. cloacae 54	250	250
E. coli 14 (hemolytic)	500	500
S. enteritidis 1	250	500
S. typhimurium 2	250	500
S. flexneri 3	250	500
P. mirabilis 33	500	500

Development of a therapeutic agent with vegetable extract in the form of tablets for gastroenterology
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Introduction. There is a progressive increase in the incidence of inflammatory diseases of the upper gastrointestinal tract. Resistance of microorganisms to most antibacterial drugs prescribed to gastroenterological patients has formed the need to search for new therapeutic agents, including extracts. Dry extract was obtained on the basis of *Sanguisorba officinalis* roots selected as the object of study. Previous biological studies have proven its gastroprotective and antimicrobial action, and a survey of pharmacy experts showed the commitment of consumers to drugs in tablets as the most popular dosage form. Therefore, the aim of the study was to develop drugs in the form of tablets for gastroenterology, based on the dry extract of *Sanguisorba officinalis* roots, which has antimicrobial action. **Materials and methods.** Objects of study involved dry extract of *Sanguisorba officinalis* roots and excipients for tableting. According to the methods of the State Pharmacopoeia of Ukraine, the pharmaco-technological properties of tablets (homogeneity of mass, abrasion, resistance of tablets to crushing, disintegration time, average weight) were studied and their appearance was visually determined. Antimicrobial activity was studied of the Biochemistry and Biotechnology Laboratory of the State Institution «Mechnikov Institute of Microbiology and Immunology of NAMS of Ukraine» under the direction of Candidate of Biological Sciences Osolodchenko T. P. by the method of double serial dilutions in nutrient broth with statistical processing of data results by Excel software. The technology of obtaining tablets on the basis of dry extract of *Sanguisorba officinalis* roots under the conditional name «Gastro-San» by the method of direct compression with the technological scheme of their production was developed. The pharmaco-technological properties of tablets were studied and the compliance of the obtained indicators with the requirements of SPU was established.

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Studies of the antimicrobial properties of Gastro-San tablets against reference test strains (*S. aureus* ATCC 25923, *E. coli* ATCC 25922, *B. subtilis* ATCC 6633, *P. aeruginosa* ATCC 27853, *P. vulgaris* ATCC 4636 and *Candida* fungi) and clinical strains of microorganisms (*S. aureus 57, E. coli 23, K. pneumonia 13, P. vulgaris 18, C. freundii 39, E. cloacae 54, E. coli 14 (hemolytic), S. enteritidis 1, S. typhimurium 2, S. flexneri 3, P. mirabilis 33*) proved antimicrobial action of the developed tablets. **Conclusions.** The technology of obtaining Gastro-San tablets by direct compression has been developed. Assessment of pharmaco-technological indicators of the developed tablets was carried out and conformity of quality of Gastro-San tablets to requirements of article «Tablets» of the State Pharmacopoeia of Ukraine was established. The antimicrobial action of the drug Gastro-San has been established, which indicates the prospects of including the developed drug in the complex therapy gastrointestinal diseases as an antimicrobial agent.
Key words: dry extract of *Sanguisorba officinalis* roots, tablets, technology, gastroenterology, antimicrobial action.

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