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Development of the technology of vials-pencils for storage and application of medicated products on the skin and its appendages

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Abstract

The formulation of "Propolis-Derma" medicated products in the form of lotions developed on the basis of the substance with the antimicrobial and antifungal action and propolis tincture has been theoretically substantiated and experimentally confirmed. The original container for new medicated products – drug markers (vials-pencils for storage and application on the skin and its appendages) has been developed; their industrial production has been tested and introduced into production on the territory of Ukraine. The flowcharts of manufacturing for vials-pencils have been introduced aiming to produce medicated products, medicinal and cosmetic antiseptics. The manufacturing normative documents for three "Propolis-Derma" cosmetic lotions have been developed and approved; conclusions of the state sanitary-epidemiological expertise of Ukraine according to DSTU 4093-2002 "Cosmetic lotions and tonics. Specifications" have been received.

Keywords: Vials-pencils, medicated products, appendages

Introduction

The beginning of the XX-th century since discovery of antibiotics gave hope to victory over causative agents of infectious diseases. However, uncontrolled use of antimicrobial drugs has led to the appearance of a large number of mutagenic forms of microorganisms with a high drug resistance [9]. Consequently, in medicine there is a need of creating effective antimicrobial agents that could be characterized, on the one hand, with a pronounced antimicrobial action to microorganisms, including antibiotic-resistant strains, without contributing to formation of the antibiotic resistance in microorganisms, and, on the other hand, would not lead to development of various manifestations of side effects on the human body [5, 8, 9, 14].

At the same time, the attention should be paid to the high proportion of mycoses in the structure of infectious pathology, and there is a tendency to their increase. According to the WHO statistics up to 30% of the adult population is affected by fungal infections [16]. Therefore, the search of modern and effective antimycotics is a topical problem of medicine and pharmacy [10, 11, 13, 15]. In this respect, biologically active substances of natural origin, in particular the products of beekeeping and their standardized substances having a wide spectrum of the pharmacological action are of particular importance [17].

Analysis of recent years shows that when treating infectious diseases using antibiotics, including those of the fungal etiology, resistant clinical strains appear, especially in the cases when the disease is caused by drug-resistant strains [1, 4, 7, 9]. In this regard, overcoming of multiple resistance is a complex and important problem of the national health. Today it is possible to solve this problem replacing medicines that have lost their pharmacological properties by new, more effective and affordable drugs. Despite the fact that such a change does not solve the problem of the antibiotic resistance as a whole since after a while other resistant strains of pathogenic bacteria and fungi can also appear to the new drugs, nevertheless, this way is considered to be promising and justified.

As aforesaid, the search for new effective domestic antifungal drugs continues to be one of the urgent problems of practical medicine since manifestations of this pathology require special approaches to development of the appropriate medicated products for the treatment of fungal infections.

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Experimental Part

In our previous studies a number of “Propolis-Derma” medicated products were developed. They are “Propolis – PSC” (RC № 3320715444-02:2016), “Propolis – PCD” (RC № 3320715444-01:2016) and “Propolis – PNH” (RC № 3320715444-03:2016) with the antifungal, antimicrobial and keratolytic action created according to DSTU 4093-2002 "Cosmetic lotions and tonics. Specifications" for treating dermatomycoses, pityriasis versicolor, as well as diseases caused by yeast-like fungi of *Candida* genus [2, 3, 6]. It has been found that the pharmaceutical compositions proposed do not exhibit side effects, comply with the requirements of the State Pharmacopoeia of Ukraine (SPhU) and can be used to treat mycoses in conditions of high resistance of fungi to traditional antifungal drugs [12].

The aim of this work was to develop the technology of vials-pencils for storage and application of “Propolis-Derma” medicated products on the skin and its appendages. The compositions of the antiseptic medicated products proposed in the form of lotions (alcohol-water solutions) in original containers are provided for use on damaged and healthy areas of the skin for first aid and emergency medical care and preventive and treatment procedures.

As a container for our “Propolis-Derma” products (Propolis – PSC, Propolis – PCD and Propolis – PNH) a new type of medical products – vials-pencils for storage and application of drugs on the skin and its appendages was used. They comply with the requirements of technical specifications (TS) 25.2-2094621496-001-2004 "A vial-pencil for storage and application of drugs" and are used in clinical and inpatient departments of medical institutions, outpatient departments, medical aid stations, injury care centers in the first-aid kits for personal use.

At the first stage of the experimental studies the tests regarding the possibility of introduction and application of alcohol-water solutions of “Propolis-Derma” medicated products in vials-pencils on the skin were conducted, and their compliance with the requirements of TS 25.2-2094621496-001-2004 "A vial-pencil for storage and application of drugs" was checked. The experimental samples of “Propolis-Derma” alcohol-water solutions were introduced in vials-pencils of FK-132 and FK-92 grades meeting the requirements of a set of documents according to specification KLLV 2094621496001 and the reference standard approved in the appropriate order. The appearance and size of the vials-pencils of FK-132 and FK-92 grades are presented in Fig. 1 and 2.

The test results of the experimental samples of vials-pencils filled with “Propolis-Derma” solutions on compliance with the

requirements of TS 25.2-2094621496-001-2004 are given in Tab. 1.

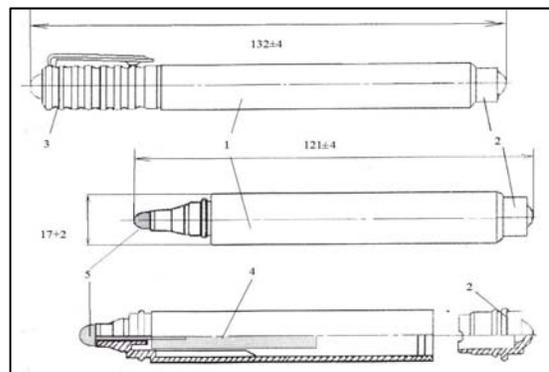


Fig 1: The appearance and size of a FK-132 vial-pencil (1 – body; 2 – plug; 3 – cap; 4 – storage unit; 5 – stick)

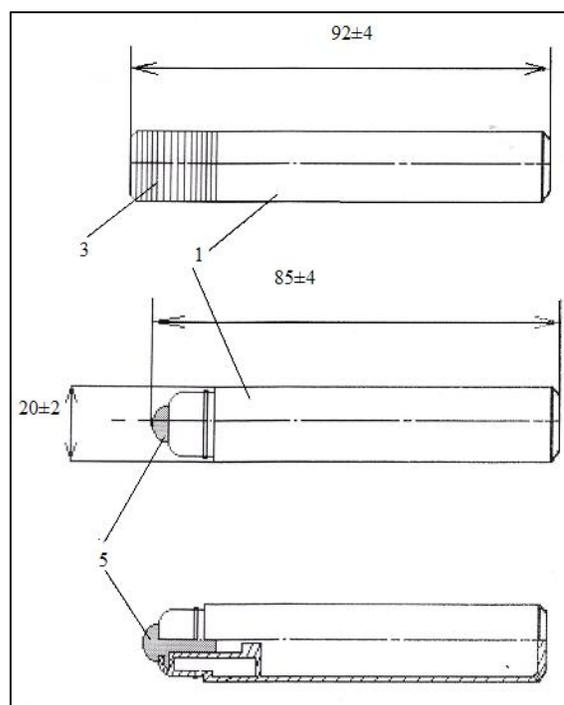


Fig 2: The appearance and size of a FK-92 vial-pencil (1 – body; 3 – cap; 5 – stick)

Table 1: The test results of the solutions with “Propolis-Derma” medicated products introduced in vials-pencils on compliance with the requirements of TS 25.2-2094621496-001-2004 “A vial-pencil for storage and application of drugs”

The name of the test	Requirements of TS 25.2-2094621496-001-2004	Test results	
		FK-132 vial-pencil	FK-92 vial-pencil
Control of the sizes	According to TS	Satisfied	Satisfied
Control of the amount of drug substances	The amount of the antiseptic drug introduced – 3 ml	Satisfied	Satisfied
Control of materials	According to TS	Satisfied	Satisfied
Quality control of the surface and the absence of impurities	According to TS	Satisfied	Satisfied
Leakage test	According to TS	Satisfied	Is not satisfied
Control of packing	According to TS	Satisfied	Satisfied
Control of labeling	According to TS	Satisfied e	Satisfied
Control of the product	Manufacturer: “Apitek-A” Ltd., batch 010914	Satisfied	Satisfied

Tab. 2 presents materials of standard grades for manufacturing the components of vials-pencils.

Table 2: Materials for manufacturing vials-pencils

The name of the vial component	The material used
Body	Polyethylene of 15803-020 grade, best quality according to GOST 16337 or polyethylene of 277-73 grade, best quality according to GOST 16338
Cap	Polypropylene or propylene copolymer of 21060 grade, best quality according to GOST 26996
Plug	Polypropylene or polypropylene copolymer of 21060 grade, best quality according to GOST 26996 or polypropylene "Li-pol", TS 54008400.001-97
Capillary storage unit	Polyester XPE 434247 by "Filtrona fileter GmbH", Germany
Capillary stick	Polyethylene by "Porex Technologies GmbH", Germany
Cover of the storage unit	Polypropylene by "Filtrona fileter GmbH", Germany

Results and Discussion

Data in Tab. 1 indicate that basically "Propolis-Derma" medicated products introduced in vials-pencils of FK-132 and FK-92 grades for storage and application on the skin meet the requirements given in TS 25.2-2094624496-001-2004 by the parameters of tests and quality control. However, the experiment revealed an insufficient hermiticity of vials-pencils of FK-92 grade, therefore, for further studies vials-pencils of FK-132 grade were selected.

The manufacturing process of vials-pencils containing "Propolis-Derma" medicated products consists of several main stages:

Stage 1. Sanitization and preparation for manufacture.

Stage 2. Preparation of solutions.

Stage 3. Purification of the solutions obtained.

Stage 4. Quality control and standardization of medicated products.

Stage 5. Dispensing, packing, and labeling.

Stage 1. Sanitization and preparation for manufacture

Stage 1.1. Preparation of manufacturing premises

A manufacturing premise must meet the requirements of the instruction "Requirements for prevention of microbial contamination of products when manufacturing non-sterile medicines in enterprises and organizations of chemical and pharmaceutical industry". The entrance of persons who are not related to the manufacturing process to the manufacturing premise is strictly prohibited. The movement of the staff without production necessity is limited.

Smoking and eating is forbidden in manufacturing premises. Daily after cleaning the equipment and revealing the residues of the raw material the floor and walls are thoroughly washed with special disinfectants permitted for use. The labeled materials and equipment are stored in a special cabinet.

Stage 1.2. Preparation of disinfecting solutions

Disinfecting solutions are used for treating hands of the personnel, equipment and surfaces. These solutions are prepared in a specially isolated room and filtered to prevent particulate contamination. Bottles with disinfecting solutions are stored in a closed room specially designed for the purpose. As disinfecting solutions the alcohol hydrogen mixture in the concentration of 76–80%, solutions of hydrogen peroxide in the concentration of 1–6% with 0.5% chlorhexidine solution are used. It is recommended to replace disinfecting solutions every week in order to avoid appearance of resistant strains of microorganisms.

Stage 1.3. The process of sanitization and preparation for manufacture

When carrying out the manufacturing process for vials-pencils,

and in order to provide the high quality for the finished product the personnel must observe the rules of occupational and personal sanitation and safe working conditions to eliminate microbial contamination of medicated products during production, storage and transportation.

Stage 1.4. Preparation of equipment

Before starting the shift foreman checks the readiness of equipment to work: the absence of residues of the raw material and semi-finished products, equipment integrity and cleanness of its working parts, the presence of labels indicating the name, batch, release date, surname and initials of the operator. After completing the work the operator cleans the equipment used during the manufacture in accordance with the instructions. Containers and equipment must be periodically subjected to washing, cleaning and disinfection.

Stage 1.5. Preparation of the staff

According to the instruction "Manufacture of medicines. The staff of pharmaceutical enterprises. Basic requirements" the personnel should be dressed in the cleanroom garment (a gown, a jacket, trousers or overalls, a cap that completely covers the hair), it is necessary to have respirator or mask, rubber gloves, shoes or shoe covers. In the cloakroom of the overclothes the staff takes off the streetwear, footwear, puts shoes on and goes to the room with the cleanroom garment. The staff keeps the personal belongings in lockers. The cleanroom garment is stored in separate cabinets. Wearing the cleanroom garment the treatment of hands must be done by the personnel. At least once per year there is a briefing on the rules of personal hygiene and health check-up of the staff.

Stage 2. Preparation of solutions

Stage 3. Purification of the solutions obtained

According to the degree of purification solutions are one of the most imperfect. The low temperature in the room reduces the solubility of ballast substances in solution and their sedimentation. Coagulation and precipitation of a significant amount of high-molecular compounds, as well as various particulate contamination are possible when settling. The stepwise control of the solutions obtained on the content of active substances or a dry residue, as well as the alcohol concentration is also carried out, and, if necessary, these indicators are corrected. The solutions obtained are also filtered. Filtration is carried out under vacuum or under pressure with the use of a druck filter or press filter.

Stage 4. Quality control and standardization of medicated products

The quality of the solutions obtained is controlled by the following indicators:

Organoleptic properties: Solutions should be transparent and keep the original odor of the substances included in the composition of medicated products.

The analysis of the content of active substances: For this purpose qualitative and quantitative chemical, physicochemical and biological analyses are carried out. The content of the substances medicated products is expressed in %. In case of the increased content of active substances the solution is diluted with a pure solvent.

Standardization by dry residue.

By the content of ethanol: This test is carried out with each sample of the medicated product. Ethanol is determined by distillation according to the boiling point. The concentration of ethanol must always be below the initial solution since ethanol is partially evaporated in the process of production. With the proper observance of the manufacturing process the concentration of ethanol will be within permissible tolerance, and in case of its nonconformance the concentration of alcohol will be naturally lower than the required concentration, therefore, in this case the sample is discarded.

Alcoholometry: It is carried out using a pycnometer or an areometer. The concentration partially characterizes the quality of the solution obtained.

Heavy metals: Usually the traces of heavy metals at the level of not more than 0.001% may be present. The increase in the rate of the heavy metal content indicates the use of the inappropriate equipment and poor quality water containing a high concentration of a dry residue.

Stage 5. Dispensing, packing, and labeling.

The filling technology of vials-pencils with alcohol-water solutions of medicated products

The complete components of vials-pencils include storage units, plugs, a body, a cap and a stick (i.e. capillary stick fitted in its position in the body and tightly closed by the cap). For one cycle of filling with lotions the device must be completed with 45 sets of vials-pencils, for this purpose 45 storage units are placed in 5 containers for filling (15 items in each container). The scheme of a container for filling of storage units of vials-pencils with alcohol-water solutions of medicated products is given in Fig. 3. It is a plastic vessel, which is closed with an airtight cap and a rubber stopper.

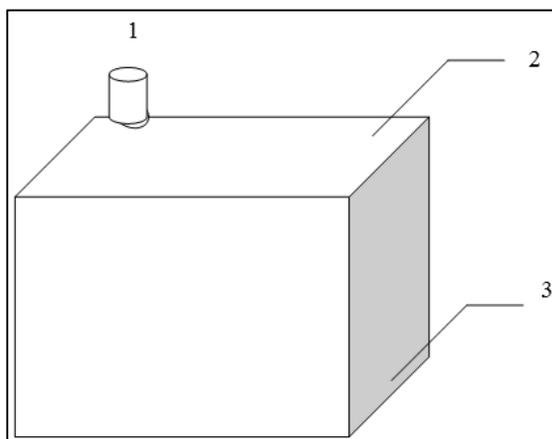


Fig 3: The scheme of a container. 1 – a rubber stopper with a filler opening; 2 – a cap of the container; 3 – the body of the container.

Inside the container there is a plate with 16 holes. The upper left hole with the diameter of 17 mm is designed for filling of the solution. The remaining 15 holes designed for the containers in which storage units are put. At the bottom of the container there is a hole with the diameter of 3 mm (Fig. 4 and 5).

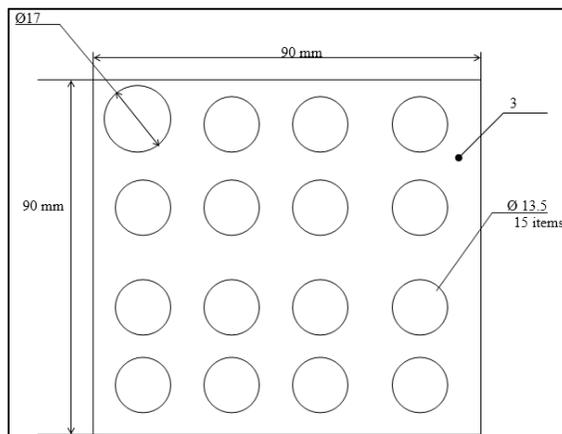


Fig 4: The scheme of the container cover. Polyethylene containers are put in a 13.5 mm hole.

Using the graduated cylinder the solution with the medicated product in the amount of 100 ml is filled into the container through the filler opening. Then the solution under the action of capillary forces through the openings at the bottom of the containers is moved into the storage unit until complete saturation. The point of complete saturation of the storage units is considered to be the surface of their upper ends fully colored with the appropriate solution. Each storage unit takes approximately 3 ml of the solution, i.e. only 45 ml per a batch of one container (15 storage units).

After completion of the exposure time the storage units are removed from the container and placed in vials-pencils. In the container the solution in the amount of 55 ml remains. At the beginning of the next cycle of filling (and all other subsequent cycles) 45 ml of the corresponding solution of the medicated product is added to the container using a proportioner. The body of the vial-pencil is closed by the plug up to the rim on the plug when slightly pressing. Then using a rubber hammer the plug is placed permanently in its place.

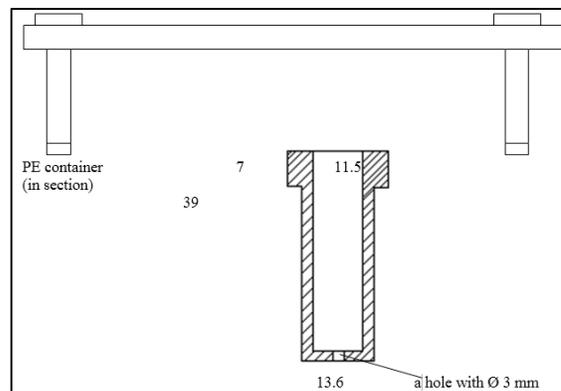


Fig 5: A polyethylene container (for storage units)

The flowcharts of manufacturing for medicated products – “Propolis-Derma” lotions filled in vials-pencils in pharmacy and industrial conditions are presented in Fig. 6 and 7.

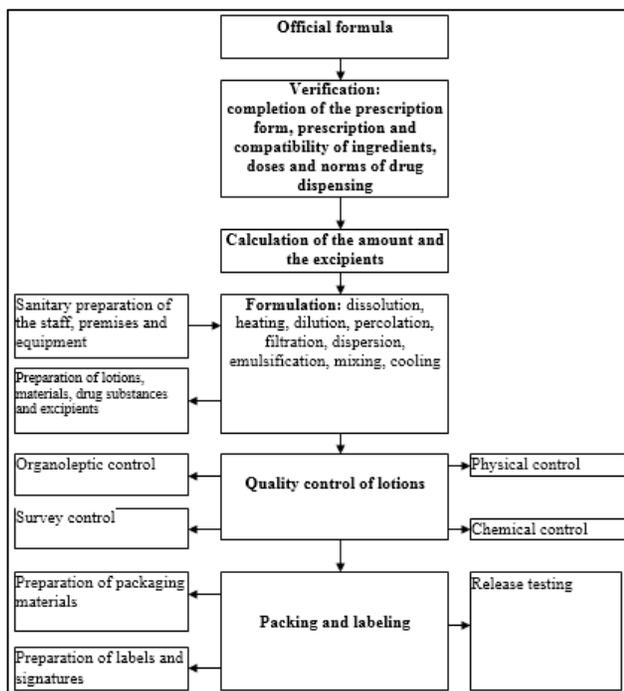


Fig 6: The flowchart of manufacturing for “Propolis-Derma” lotions in pharmacy conditions

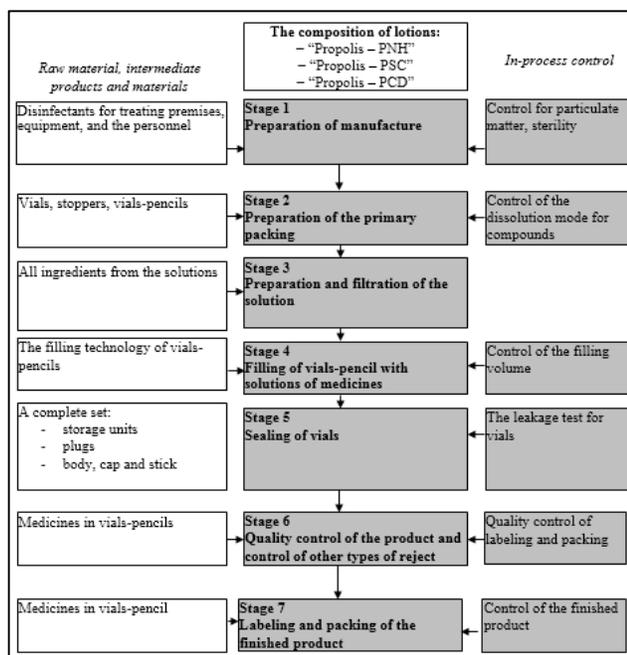


Fig 7: The flowchart of manufacturing for “Propolis-Derma” lotions in industrial conditions

Therefore, in pharmacy and industrial conditions the technology of filling vials-pencils with “Propolis-Derma” medicated products for storage and application on the skin and its appendages has been developed.

Conclusions

1. For the first time on the basis of the substance with the antimicrobial and antifungal action and propolis tincture the formulation of “Propolis-Derma” medicated products in the form of lotions filled in vials-pencils for treating mycoses has been developed.

2. The original container for new medicated products – drug markers (vials-pencils for storage and application on the skin and its appendages) has been developed; their industrial production has been tested and introduced into production on the territory of Ukraine.
3. The flowcharts of manufacturing for vials-pencils have been introduced aiming to produce medicated products, medicinal and cosmetic antiseptics.
4. The manufacturing normative documents for 3 “Propolis-Derma” cosmetic lotions: “Propolis – PSC”, “Propolis – PCD” and “Propolis – PNH” have been developed and approved; conclusions of the state sanitary-epidemiological expertise of Ukraine (No. 0.503.02.-07/22191 and 05.03.02.-04/22198 dated 30.06.2016) according to DSTU 4093-2002 "Cosmetic lotions and tonics. Specifications" have been received.

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