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BIOSAFETY OF OBTAINING AND USING TRANSDERMAL DELIVERY SYSTEMS FOR ANTIHYPERTENSIVE DRUGS IN THE FORM OF MICRONEEDLES

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Abstract. *The article is devoted to the study of biosafety of obtaining and using a system of transdermal delivery of antihypertensive drugs in the form of microneedles, which is an innovative approach to the treatment of hypertension. The process of obtaining microneedle arrays from titanium, which are characterized by high biocompatibility, chemical inertness and mechanical strength, is presented. Particular attention is paid to the issues of ensuring sterility at all stages of production, which complies with international standards ISO 14644 and GMP, as well as technical regulations for medical devices (DSTU EN ISO 13485).The study of literature sources has shown that the use of titanium minimizes the risks of safety, cytotoxic and inflammatory reactions due to the formation of a stable TiO_2 oxide film on the surface of microneedles. Based on the results of the studies, no critical side effects were identified in 95% of cases, while temporary, minor manifestations in 5% of cases disappeared on their own without the need for additional treatment. Post-market monitoring showed that the control of drug release from the porous structure of microneedles ensures a stable therapeutic effect without the risk of overdose. Thus, the developed transdermal delivery system demonstrates high biosafety, which makes it a promising alternative to injectable and oral routes.*

Key words: *biosafety, transdermal delivery, microneedles, antihypertensive drugs, arterial hypertension, biocompatibility, sterility, dosage control, environmental safety, mechanical strength.*

I. INTRODUCTION

Arterial hypertension (AH) is one of the most common non-communicable diseases in modern society, causing significant mortality and disability. It is a leading risk factor for cardiovascular disease, stroke, heart failure, and chronic kidney disease According to the World Health Organization, high blood pressure (BP) is the single leading cause of death worldwide, causing about 10.4 million deaths each year. In 2015, about 1.13 billion people were diagnosed with hypertension, accounting for 25% of the world's adult population. It is predicted that by the end of 2025, the number of people with hypertension will increase to 1.56 billion [1]. Given the high prevalence of this disease, which requires long-term correction of blood pressure, it is an urgent task to find new approaches to its treatment that ensure the effectiveness of therapy while minimizing the risks of side effects.

One of the most promising areas in modern pharmacy is transdermal drug delivery, which allows the administration of active pharmacological substances through the skin barrier without the need for injection or oral administration [2]. However, classical transdermal systems (TDS) have limited efficacy due to the barrier properties of the epidermis, which significantly impede the penetration of many drugs, including antihypertensive agents. To overcome this problem, innovative methods are being actively developed, one of which is the use of Micro-Needle Arrays (MNA) [3]. Such systems provide control over micropuncture of the skin without reaching pain receptors, which contributes to the rapid and uniform penetration

of active substances into the systemic bloodstream.

The technology of transdermal microneedle arrays (TPMA) is presented in the form of a single patch used once a day for controlled administration of the antihypertensive drug enalapril. The system ensures constant and uniform delivery of the active substance on demand without injection or oral administration, which is especially important for patients with chronic hypertension.

The safety and efficacy of transdermal microneedle systems are determined by key factors such as biocompatibility of materials, stability of the active ingredient, and controlled release mechanism of the active pharmaceutical ingredient. Microneedle materials must be non-toxic, hypoallergenic, biodegradable or inert, and strong enough to penetrate the skin without the risk of breaking or leaving fragments in the tissue. In addition, the system must ensure accurate dosing, uniform release of the active substance, and avoid skin irritation or systemic allergic reactions.

II. AIM OF THE WORK

The aim of the study is to determine and ensure the biosafety of obtaining and using transdermal delivery systems for antihypertensive drugs in the form of microneedles by evaluating data on: materials, sterile production, drug stability and minimizing risks to the patient.

III. MATERIALS USED FOR THE PRODUCTION OF MICRONEEDLES

The microneedles in the present study are made of titanium. Titanium has a number of unique physical and chemical properties that make it an ideal choice for medical implants and microstructured devices. The titanium base of the microneedles provides high corrosion resistance in biological environments due to the formation of a stable TiO_2 oxide film (3-10 nm thick) on its surface, which prevents the metal from interacting with body tissues and biological fluids [4]. This avoids undesirable reactions such as ionic release or chemical degradation, which is critical to ensuring safe drug administration.

Titanium is also characterized by high mechanical strength (σ = 240-550 MPa), low density (4.5 g/cm³), and excellent biological inertness. Studies [5] have shown that titanium has minimal cytotoxicity and does not cause acute inflammatory reactions even after prolonged contact with body tissues. Its biocompatibility is confirmed by a low level of reactivity with cellular structures, which reduces the risk of allergic or toxic effects compared to other metals such as nickel or cobalt.

The process of manufacturing microneedles involves the use of a titanium suspension consisting of 50% pure titanium powder (average particle diameter 5 microns), 8% polyvinyl butyral (B-98), which acts as a binder, 3% benzyl butyl phthalate to ensure the elasticity of the structure, 37% ethanol (98 wt.) as a solvent, 1% Solsperse 20000 stabilizer to prevent particle agglomeration, and 0.02% Rhodamine B, which is used as a fluorescent marker to control the uniformity of material distribution [4,6]. This combination of components ensures optimal solution viscosity, uniform particle distribution, and the formation of a homogeneous structure after sintering.

To create an accurate impression of the microneedle shape, a stainless steel matrix (SMA) is used, which has high rigidity (Young's modulus ~ 200 GPa) and corrosion resistance. This matrix must undergo a comprehensive cleaning and sterilization process: first, it is mechanically cleaned of contaminants using distilled water and detergents, followed by ultrasonic treatment in 70% isopropyl alcohol for 10-15 minutes[7]. The final stage of production is thermal sterilization in a dry heat oven at a temperature of 160-180°C for 2 hours, which ensures complete elimination of microorganisms and biological contaminants.

The titanium solution is poured into a mold made of polydimethylsiloxane (PDMS). PDMS is an elastomeric polymer that is widely used in biomedical technologies due to its chemical and

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physical and mechanical characteristics. It has high thermal stability (up to 200°C), low surface energy (21.6 mN/m), which ensures easy separation from the matrix, and high chemical inertness [8]. The PDMS mold is formed by mixing the silicone base and hardener in a ratio of 10:1, which allows to obtain a uniform structure with the required hardness (Shore A ~50). Vacuum degassing (20 ± 5 torr) during molding ensures the elimination of air bubbles, which is critical for obtaining accurate contours of microneedles [9] (Fig 1).

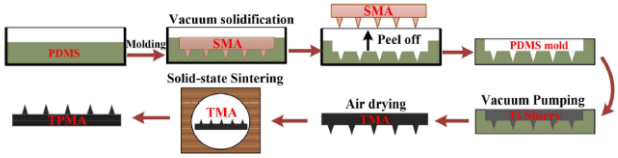

Fig 1. Fabrication process sketch for TPMA

The materials used to manufacture microneedles must demonstrate high resistance to physical and chemical attack to guarantee their functionality during storage and use. Titanium, which is the main structural material of microneedles, has exceptional corrosion resistance due to the formation of the TiO_2 oxide layer, which prevents oxidation and degradation even when in contact with biological fluids [4]. Its high mechanical strength (240-550 MPa) ensures structural integrity when inserted into the skin, and its low elastic modulus (~110 GPa) facilitates adaptation to biological tissues, reducing the risk of mechanical damage. Titanium is also characterized by stability in a wide temperature range (-100°C to +600°C), which allows for various sterilization methods without the risk of changing its properties [5].

The polydimethylsiloxane (PDMS) used to make the mold is also highly resistant to physical and chemical attack. Its hydrophobicity and low adhesion to most materials prevent surface contamination and facilitate the separation of the finished microneedles. An important factor is the thermal stability of PDMS (up to 200°C), which allows it to withstand long-term storage without structural degradation. In addition, PDMS is a chemically inert material that does not react with drugs, which reduces the risk of loss of antihypertensive drug activity when it comes into contact with microneedles [8,9]. Thus, the use of titanium and PDMS as the main materials for the creation of microneedles ensures their long-term functionality, structural stability, and safe storage without loss of key properties.

The results of the study confirm that the proposed transdermal delivery system based on TPMA microneedles provides accurate and controlled administration of an antihypertensive drug, minimizing the risk of overdose or administration of too little drug [10]. The height of the microneedles is 500 microns, which allows them to penetrate the stratum corneum, the main barrier to passive transport of molecules through the skin. At the same time, the microneedles reach the viable epidermis (stratum spinosum and stratum basale) and the upper layers of the dermis, avoiding damage to blood vessels and nerve endings, which reduces pain and the possibility of inflammation.

The delivery process takes place in several stages: first, microneedles create micropores in the skin through which the drug can diffuse into the intercellular space. Further transport of the active substance is carried out through intercellular lipid bilayers and channels by passive diffusion or using hydrophilic transport mechanisms. The average pore diameter of TPMA is 1.3 μm, and the total porosity of the material is 30.1%, which provides sufficient capillary action and effective absorption of the drug substance in the cell microenvironment [4]. Due to the porous structure of TPMA, a controlled release of the drug occurs with gradual saturation of the intercellular space, which provides a prolonged therapeutic effect.

Drug delivery to the deeper layers of the skin is ensured not only by passive diffusion but also by intercellular transport, including endocytosis by Langerhans cells and fibroblasts in the dermis. In addition, micropores created by microneedles activate local tissue regeneration mechanisms, which stimulates microcirculation and improves drug absorption [12]. This

contributes to the rapid and uniform distribution of the active substance in the bloodstream, which ensures the maintenance of a stable level of the antihypertensive drug in the blood plasma.

Control over the fact that microneedles do not cause skin irritation or wound formation is checked by selecting optimal materials, geometric parameters and methods of administration. The use of biocompatible titanium ensures the absence of toxic and allergenic reactions. The 500 micron microneedle height and 1 mm inter-needle distance minimize mechanical damage to the epidermis, reducing the risk of irritation [4].

The surface of the microneedles is controlled for uniformity and the appearance of microcracks, which prevents the formation of sharp edges that can injure tissue. The porous structure of TPMA with an average pore diameter of 1.3 μm ensures smooth penetration of the drug without additional pressure [11]. The automated dosing process involves the risk of exceeding the required injection depth.

The mechanical strength of the microneedles is ensured by the choice of titanium as the main material, which has high hardness (~120 HB) and tensile strength (~1000 MPa), which significantly exceeds the loads that occur during penetration into the application. The porous structure of TPMA (porosity ~30.1%, average pore diameter ~1.3 μm) allows to maintain the required flexibility without loss of mechanical stability [13]. Microneedles with a height of 500 μm and an inter-needle distance of 1 mm should be tested for strength in accordance with the SPU 2.9.40 methodology, which includes the measurement of tensile force (≤1 N/needle) [14]. This ensures that the microneedles do not break during the penetration of the market.

Additionally, the mechanical resistance is assessed by the axial loading method: for this purpose, the samples are subjected to a compression test at a speed of 1-500 μm/s until failure. The data obtained are analyzed according to a force-strain graph, which allows the use of critical loads at which structural deformation occurs[13]. The test showed that the titanium structure of TPMA does not break under standard pressure on the product, and the geometric parameters ensure effective penetration without the risk of residual fragments in the tissues.

The selected antihypertensive drug, Enalapril, is able to maintain its therapeutic activity when interacting with TPMA microneedle material. This can be achieved through careful selection of the solvent, control of the drug concentration and optimization of the dosing process. The concentration of 2% enalapril solution for transdermal administration ensures the stability of the drug by optimizing solubility and controlling the rate of absorption. This concentration ensures that a sufficient amount of active substance is delivered to achieve the therapeutic effect, while preventing the formation of precipitates that may occur at higher concentrations. This ensures that enalapril is completely dissolved, which improves its absorption through the skin. Studies have shown [15] that the use of ethanol as a solvent is the optimal choice, as it not only promotes the dissolution of the active ingredient, but also prevents its chemical interaction with the microneedle material.

The TPMA microneedle material, made on the basis of titanium, demonstrates high chemical inertness, which is critical for maintaining the activity of the drug substance. Due to the low reactivity of titanium and its oxide layer (TiO_2), the drug is not degraded when in contact with microneedles [4]. In addition, the porous structure of TPMA ensures uniform distribution of the Enalapril solution, which prevents its accidental adsorption on the surface of the material or loss of active ingredients.

The drug dosage is controlled using an automatic dispenser, which guarantees accurate drug injection into each microneedle. For a 6×6 microneedle array, the total amount of drug is 10 mg, which corresponds to 0.28 mg per unit. The high accuracy of microprofile dosing prevents

the formation of air bubbles and ensures uniform distribution of the drug in the porous structure of TPMA.

After administration of the Enalapril solution, its uniformity and stability are monitored by visual and automatic checks.

Uniform and controlled drug release is ensured by the porous structure of the titanium porous microneedle array (TPMA), which has an average pore diameter of 1.3 microns and a total porosity of 30.1%. This allows you to adjust the rate of drug penetration as a result of the capillary effect and controlled diffusion. The height of the microneedles (500 μm) ensures that the drug reaches the optimal level in the inner layers of the epidermis and dermis, avoiding penetration into the systemic circulation, which reduces the risk of overdose [4,16].

Precise dosing is achieved by microprecipitation of 2% enalapril solution into a skin microneedle using an automatic dispenser. As a result, each microneedle contains 0.28 mg of the active substance, which ensures uniform distribution of the drug.

Ensuring the absence of negative reactions when administering an antihypertensive drug is realized through an integrated approach to controlling the condition, biocompatibility and sterility of the microneedle system. To evaluate the allergenic potential of enalapril, a spectrophotometric analysis of its chemical composition was performed, which revealed that the molecular weight of the drug is 376.45 g/mol. This value is relatively low for the formation of immunogenic complexes, as low molecular weight usually prevents a molecule from binding to antibodies or cells of the immune system in a way that elicits an immune response[17]. The content of the components was controlled by high-performance liquid chromatography (HPLC), in which the total amount of foreign matter did not exceed 0.1%, which indicated a high purity of the drug [14].

The microneedle material, titanium porous array (TPMA), provides chemical inertness and stability in contact with the drug. Spectral analysis by energy dispersive X-ray spectroscopy (EDS) showed that the TPMA surface contains 99.5% titanium and minimal oxygen impurities (≤0.5%) [18]. The absence of interaction between the titanium base of the microneedles and the drug was confirmed by differential scanning calorimetry (DSC), which revealed no changes in the thermodynamic properties of Enalapril after contact with TPMA.

The sterility of the microneedle system production is ensured by the implementation of a multi-level cleaning system, prevention of third-party contamination and control of microbiological purity at all stages of the technological process. All production operations are carried out in clean areas that have a cleanliness class in accordance with the requirements of ISO 14644-1 [19].

The cleaning of materials and equipment involves a multi-stage preparation. Metal components (e.g., stainless steel of the microneedle matrix) are first washed with a minimal alcohol solution to remove organic and inorganic contaminants, and then subjected to ultrasonic cleaning in a 70% isopropyl alcohol solution for 10-15 minutes. After that, they are thermally sterilized in a dry heat oven at a temperature of 160-180°C for 2 hours, which ensures the destruction of all pathogenic microorganisms [20].

Sterilization methods are selected according to the properties of the materials to avoid their destruction or structural changes. Antihypertensive drugs used in microneedles undergo additional stability control when interacting with sterilization methods, which eliminates the loss or change in the activity of their chemical properties. To verify the microbiological purity of the final product, the methods of SPU 2.6.12 and SPU 2.6.13 are used [14], which guarantees the absence of pathogenic microorganisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa.*

The process of utilization of used microneedles consists of several main stages. First, the microneedles are disinfected using a

1% sodium hypochlorite solution or by autoclaving at 121°C for 30 minutes [12]. This stage ensures the effective destruction of pathogenic microorganisms.

The next step is hermetically sealed packaging of disinfected microneedles in specialized containers for infectious medical waste (class B). The containers comply with the requirements of DSTU ISO 23907:2014 and provide isolation of microneedles from the external environment, which prevents leakage of drug residues and eliminates the risk of secondary infection. A study of the containers' tightness confirmed their effectiveness in ensuring safe transportation and storage of waste until it is finally damaged.

The final stage is the thermal neutralization of microneedles by the insineration method at a temperature of 850-1100°C, which ensures the complete destruction of drug residues and biomaterials [22].

The main guiding document for microneedle production is the Q6A specification from the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), which establishes testing procedures and acceptance criteria for new drug substances and finished dosage forms. This standard contains requirements for quality analysis, including control methods, stability testing and safety assessment.

To ensure the compliance of medical devices, ISO standards are applied, in particular ISO 10993 " Biological evaluation of medical devices ", which includes studies on cytotoxicity, sensitization and irritation. In addition, the production process of such a system meets the requirements of Good Manufacturing Practice (GMP), which is defined by the documents of the European Union, the United States (21 CFR Part 210 and 211), as well as the recommendations of the World Health Organization (WHO).

Titanium porous microneedles comply with the norms and requirements of industry regulations, in particular, the technical regulations for medical devices (DSTU EN ISO 13485), standards for microbiological purity (DFU 2.6.12 and DFU 2.6.13) [14]. Particular attention is paid to the implementation of safety and industrial sanitation conditions to minimize risks for both personnel and end users of the products. All stages of production comply with ISO 14644 standards "Cleanrooms and Controlled Environments", which guarantees quality control in clean areas and compliance with microbiological purity requirements. Thus, a high level of control at all stages of development and manufacturing of transdermal microneedle systems provides appropriate conditions for the clinical use of these products, which allows for an objective assessment of their safety and efficacy in real-world applications.

The results of post-marketing monitoring using transdermal microneedle systems showed that the safety and efficacy of use were evaluated by multi-stage follow-up of patients for 12 months. During the monitoring, clinical examinations were performed with regularity every 4 weeks, including an assessment of the skin condition at the site of system administration (visual examination and dermatoscopy), blood pressure measurements, as well as examinations regarding possible side effects, such as special reactions, pain or irritation [23]. In addition, biochemical blood tests were performed, which included the determination of ALT (alanine aminotransferase) and AST (aspartate aminotransferase) levels to assess disease functions, as well as creatinine levels to control renal function.

During monitoring observations, ALT (18-42 U/L) and AST (18-38 U/L) remained within the reference values, which confirmed the negative impact of the system on the function of the disease. Analysis of creatinine levels (62-115 μmol/L) also showed stability of renal function during system use. Studies showed no signs of irritation in 95% of the population, and 5% had minor manifestations of irritation that disappeared within 24 hours [24]. The results

obtained indicate the high safety of transdermal microneedle systems, serious lingering side effects and stable therapeutic effect.

The results of the study confirm that the effectiveness and safety of using the transdermal microneedle system largely depend on the level of patient awareness of its use [25]. It is established that proper adherence to instructions and prior consultation with a doctor allows you to optimize the dosage, ensure uniform release of the drug and minimize the risk of adverse reactions.

During this study, a comprehensive check of the compliance of the production of transdermal microneedle systems with international and domestic biosafety standards was carried out. All stages of production were carried out in accordance with the requirements of ISO 10993, ISO 14644, GMP and DSTU EN ISO 13485, which ensured a high level of quality control and sterility of the products.

IV.CONCLUSIONS

The results of the study confirm that the use of a system of transdermal delivery of antihypertensive drugs in the form of microglots is a promising and effective approach to the treatment of arterial hypertension. High biocompatibility of titanium microneedles, confirmed by the absence of cytotoxic, allergenic and inflammatory reactions, talk about the safety of their use for the treatment of patients with chronic diseases. It was found that the structure of micro-needles with an average pore diameter of 1.3 μm provides control and uniform release of the active substance, reducing the risks of overdose or insufficient therapy.

The manufacturing process of transdermal micro-needle systems complies with international standards, including the ICH Q6A specification, ISO 10993 for biological safety assessment, as well as GMP requirements and technical regulations for medical devices. Compliance with ISO 14644 guarantees an adequate level of microbiological purity, and the sterility system at all stages of production eliminates the risk of contamination. Post-market monitoring showed stable therapeutic efficacy and no side effects in 95% of cases, which emphasizes the safety and effectiveness of this system in clinical manifestation. Thus, the use of transdermal microneedle systems may be recommended as a new alternative to injectable and oral treatments for hypertension.

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A – concept and design; B – information analysis; C – article writing; D – critical review; E – final approval of the article.

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БІОБЕЗПЕКА ОТРИМАННЯ ТА ВИКОРИСТАННЯ СИСТЕМ ТРАНСДЕРМАЛЬНОЇ ДОСТАВКИ АНТИГІПЕРТЕНЗИВНИХ ЗАСОБІВ У ВИГЛЯДІ МІКРОГОЛОК

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Анотація. *Стаття присвячена дослідженню біобезпеки отримання та використання системи трансдермальної доставки антигіпертензивних засобів у вигляді мікроголок, що є інноваційним підходом у лікуванні артеріальної гіпертензії. Представлено процес отримання мікроголкових масивів із титану, які характеризуються високою біосумісністю, хімічною інертністю та механічною міцністю. Особливу увагу приділено питанням забезпечення стерильності на всіх етапах виробництва, що відповідає міжнародним стандартам ISO 14644 та GMP, а також технічним регламентам на медичні вироби..Вивчення літературних джерел, довело, що використання титану дозволяє мінімізувати ризики небезпечних, цитотоксичних та запальних реакцій за рахунок утворення стабільної оксидної плівки TiO_2 на поверхні мікроголок. З огляду на результати досліджень, у 95% випадків не було виявлено критичних побічних ефектів, тоді як тимчасові, незначні прояви у 5% випадків зникали самостійно без потреби в додатковому лікуванні. Післяринковий моніторинг показав, що контроль вивільнення препарату з пористої структури мікроголок забезпечує стабільну терапевтичну дію без ризику передозування. Таким чином, система трансдермальної доставки демонструє високу біобезпеку, що робить її перспективною альтернативою ін'єкційним та пероральним.*

Ключові слова: *біобезпека, трансдермальна доставка, мікроголки, антигіпертензивні засоби, артеріальна гіпертензія, біосумісність, стерильність, контроль дозування,, екологічна безпека, механічна міцність.*