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Liquid plasters (skin glues) as a modern promising means for the treatment of wounds

Los emplastos líquidos (colas cutáneas) como un medio moderno y prometedor para el tratamiento de heridas

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SUMMARY

The study of technological aspects and modern approaches to developing a liquid patch (skin glue) for the treatment of wounds has a significant impact on the development and improvement of the direction of soft medicinal forms for dermal application. The skin is a natural physical barrier that protects the tissues and organs located under it. Using a liquid plaster in the therapy of wound processes of various aetiologies is a modern alternative to the classical methods of applying sutures, bandages, and various plasters. **Objective:** *This work aims to generalize the prospects of using liquid plasters (skin adhesives), the features of their technology, and quality control methods.* **Method:** *To achieve the goal, methods of analysis, synthesis, comparison, and generalization were used.* **Results:** *The results were the study of the peculiarities of the formulations of liquid plasters, which include active pharmaceutical ingredients (APIs) and auxiliary substances that form the basis of the medicinal product in the form of liquid glue. Features of the composition of the liquid patch were determined by the specifics of the anatomical structure and functions of the skin to assess the bioavailability APIs and therapeutic effectiveness of developed liquid plasters presented on the market of Ukraine and European countries. The data analysis on the wound healing process made it possible to determine the dosage form's choice, ensure a longer and prolonged effect, and accelerate the wound healing process.*

Keywords: *Soft dosage forms, film-forming system, plasticizer, prolonged action, active pharmaceutical ingredients.*

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RESUMEN

El estudio de los aspectos tecnológicos y los enfoques modernos para el desarrollo de un parche líquido (pegamento cutáneo) para el tratamiento de heridas tiene un impacto significativo en el desarrollo y la mejora de la dirección de las formas medicinales blandas para aplicación dérmica. La piel es una barrera física natural que protege los tejidos y órganos ubicados debajo de ella. El uso de un parche líquido en la terapia de procesos de heridas de diversas etiologías es una alternativa moderna a los métodos clásicos de aplicación de suturas, vendajes y el uso de varios parches. **Objetivo:** *El propósito*

de este trabajo es generalizar las perspectivas de uso de parches líquidos (adhesivos cutáneos), las características de su tecnología y los métodos de control de calidad. **Método:** *Para lograr el objetivo, se utilizaron métodos de análisis, síntesis, comparación y generalización*. **Resultados:** *Los resultados el estudio de las peculiaridades de las formulaciones de parches líquidos, que incluyen ingredientes farmacéuticos activos (API) y sustancias auxiliares que forman la base del medicamento en forma de pegamento líquido. Las características de la composición del parche líquido se determinaron en función de las particularidades de la estructura anatómica y las funciones de la piel para determinar la biodisponibilidad de los principios activos y la eficacia terapéutica de los parches líquidos desarrollados que se presentan en el mercado de Ucrania y los países europeos. El análisis de los datos sobre el proceso de cicatrización de heridas permitió determinar la elección de la forma farmacéutica, para garantizar un efecto más prolongado, y para acelerar el proceso de cicatrización de heridas*.

Palabras clave: *Formas farmacéuticas blandas, sistema filmógeno, plastificante, acción prolongada, ingredientes farmacéuticos activos*.

INTRODUCTION

One of the most important tasks of modern pharmacy is developing and introducing new medicinal forms that show effective therapeutic and curative effects directly in the affected part of the body (1). Modern pharmaceutical technologies make it possible to develop innovative dosage forms for treating wounds in the form of a liquid patch (skin glue) (2). Many skin injuries are superficial and small in area, which do not significantly affect the patient's health, but at the same time, require the necessary therapeutic and preventive manipulations (3). Such injuries include abrasions, cuts, microtrauma, and thermal and chemical damage to the surface layer of the skin.

Liquid plasters are widely used as a sterile dressing material in inpatient and outpatient treatment in gynecology since the specific localization of the wound (in the perineum) makes applying an aseptic bandage or a bandage with medicine is impossible (4). In particular, it is used in the post-partum period to achieve a local anti-inflammatory effect, which contributes to the rapid healing of post-partum injuries, the prevention of the development of infectious diseases, and the reduction of pain. Therefore, one of the promising areas of modern obstetrics is using a liquid patch in clinical practice (5). The development of this assortment group of drugs is aimed at improving the properties of the drug in the form of a liquid patch by eliminating several disadvantages that arise when using a traditional patch, namely the greenhouse effect, insufficient or excessive adhesion (depending on the stickiness of the base), water permeability. Liquid plasters have several advantages compared to other medicinal forms for dermal application (6). Applied directly to the affected area, they provide prolonged release of active pharmaceutical ingredients (APIs). After evaporation of the solvent, the concentration of APIs in the film increases several times, which leads to an increase in the concentration gradient and, accordingly, better penetration into the skin. The formed film serves as a barrier for reinfection and prevents the transfer of mycelial cells. The liquid plasters are easy to use; they are atraumatic and do not cause pain when applied. They also keep the wound in a moist environment, strengthen reepithelialisation and collagen synthesis, promote angiogenesis, create hypoxia in the wound bed, and reduce the wound bed's pH, decreasing wound infection.

Like any medicinal product, liquid plaster production and development go through all life cycle stages. Compliance with Pharmacopeia's requirements, a collection of official documents (standards and regulations) that ensures the proper quality of medicinal products, plays a significant role in regulating the circulation of medicinal products in the global and national pharmaceutical markets. The problem of this analysis is the lack of unified requirements for determining indicators and their norms for soft medicinal forms, namely medicinal products in the form of a liquid patch. Therefore, it is important to consider the requirements of the Ukrainian Scientific Pharmacopoeia Center for the Quality of Medicines and compare them with the data of world pharmacopeias regarding indicators and their norms, as well as methods and methods that determine the quality of liquid plasters as a dosage form (7).

The published work of Orlovetskaya et al. gives the technology of preparation of soft dosage forms – a liquid patch according to

the prescription of Czerniak (8). The authors provided detailed step-by-step instructions for creating a liquid plaster and reviewed the historical background of its creation. Examples of the main substances included in the composition of liquid plasters and substances that ensure their elasticity and plasticity were given. In the study by Blazhko et al., modern requirements of the leading pharmacopeias for the characterization, quality control, and classification of soft dosage forms were considered and compared (9). The conducted comparative study was based on the analysis of the approach of the Ukrainian Scientific Pharmacopoeia Center for the Quality of Medicines and foreign pharmacopeias to the soft dosage forms produced in the pharmacy.

Vons et al. conducted a comparative analysis of medicinal products for the local treatment of wounds in the Ukrainian and foreign markets (10). The researched medicinal products are registered in the territory of Ukraine, France, and Georgia. Plasters and liquid plasters were considered in more detail as means for local treatment of wounds. The study of drugs was carried out according to the State Register of Medicines and Anatomical Therapeutic Chemical (ATC) classification system. In the work of the authors, in addition to comparing the characteristics of medicinal products and the requirements for the technology of their production, considerable attention was paid to marketing information regarding the range of these drugs on the pharmaceutical markets of each of the three countries, so the results of this study can only be partially used to determine the technological aspects of the development of a liquid patch.

In the study conducted by Sangnim et al., developing and evaluating a liquid patch with *Chromolaena odorata* plant extract was studied for wound healing (11). This medicinal product was developed by extracting the leaves of *Chromolaena odorata* using the ethanol maceration technique. The effectiveness of the liquid patch with the extract of the specified plant was evaluated by testing the antioxidant activity, which consisted of the absorption of free radicals and the blood coagulation activity.

Zhao et al. conducted a study describing the development of a gel-liquid patch and evaluated its transdermal penetration *in vitro* (12). The tests showed that adding an essential oil or a microemulsion of such an oil improves the transdermal absorption of the active substance, which increases the effectiveness of this medicinal product. According to the authors' conclusions, developing a gel-liquid patch technology meets the requirements for medicines in this direction. It has several advantages, including appearance, high level of adhesion, and gradual release of the active substance, which allows reducing the number of applications of the medicine.

This study aims to comprehensively examine liquid plasters as a modern, promising means for wound treatment, focusing on their technological aspects and quality control methods. The main objectives of this research include analyzing the composition and formulation of liquid plasters, comparing the quality control requirements for liquid plasters across different pharmacopeias, and investigating the mechanism of action of liquid plasters in relation to skin structure.

MATERIALS AND METHODS

This study was conducted using the methods of analysis and synthesis, which were applied to the research object, as well as the comparison and generalization of the obtained information. The method of analysis and synthesis was chosen to provide a comprehensive study of the technological aspects of developing a liquid patch for treating wounds. A comparison approach helped determine the differences between the requirements for the development technology of these medicinal products listed in Ukraine's regulatory and technical documents and the countries selected for the study. A generalization method was applied to justify the obtained results and conclusions regarding the practicality of the unification of the researched requirements for these medicinal products.

As a result of the analysis of the research object, considering the skin's anatomical features, the liquid patch's influence on physiological processes and the therapeutic effectiveness of this medicine were considered. In this aspect, the main attention was paid to the main characteristics of the liquid patch, which include

composition, dosage form, pharmacotherapeutic group, pharmacodynamic and pharmacokinetic properties, clinical characteristics, and application features. Considering the indicated purpose of the study, special attention was paid to the composition of the medicinal product, namely its basis, which forms the given dosage form. In this direction, auxiliary substances (film-forming systems, solvents in film-forming systems, plasticizers) included in the base, their functions, and their characteristics were analyzed in detail. The search for materials for the analysis was carried out in the electronic database of medical and biological publications, PubMed (for searching English-language sources) and Google Scholar (for Ukrainian-language sources).

For the subsection describing the structure of the skin, the search keywords were used: "skin", "skin structure", "skin layers", "skin barrier", "paths of substance penetration into the skin". A total of 10 sources were selected. For the subsection describing the skin healing process, the following keywords are used: "healing stages", "homeostasis", "inflammation", "oedema", "regeneration", "scar", "factors affecting the healing process". 10 sources have been selected. In the subdivision where the composition of the liquid patch was studied, the search was conducted using the keywords: "film-forming system", "plasticizer", "solvent of the film-forming system", and "polymer for the film-forming system". Seven relevant publications were selected. A total of 27 scientific sources from 2008 to 2022 were involved in the analysis. After analyzing the received information, a database was formed to describe the technological aspects of developing a liquid plaster for treating wounds.

The comparison method was used to identify the difference between the requirements for quality control of the researched medicinal product in Ukraine, the European Union (EU), Great Britain, and Japan, using each country's regulatory and technological documents that regulate this process. When choosing countries for comparison, attention was paid to the presence in the provisions of regulatory documents (State Pharmacopoeia) of quality requirements relating to this particular medicinal product because the harmonization of pharmacopoeial requirements for medicinal products is an inevitable process in the integrated conditions of their use and one of the ways of developing pharmacopoeial standards. The following materials were used to implement this method: pharmacopoeial articles, which include requirements for the quality of soft dosage forms in the form of a patch in Ukrainian Scientific Pharmacopoeia Center for the Quality of Medicines (7), Council of Europe (13), Medicines and Healthcare products Regulatory Agency (14) and Ministry of Health, Labour and Welfare (15).

Using the generalization method, materials on the effectiveness of wound treatment with modern medicines in the form of a liquid patch were reviewed. Prospects for developing this dosage form and new directions for its use were also considered. Considering the difference in the quality requirements of the researched medicinal products specified in the pharmacopoeial articles of Ukraine, Europe, Great Britain, and Japan, the practicality of a single unified system to ensure quality control of these medicinal products on the international pharmaceutical market was determined.

RESULTS AND DISCUSSION

Requirements for quality control of soft dosage forms in the form of a patch in Ukraine, the EU, Great Britain, and Japan

Requirements for the quality of medicinal products are controlled by regulatory and technical documents developed separately by each country (16). Their observance ensures the appropriate quality of drugs, improves indicators in the healthcare field, and develops the country's pharmaceutical market, particularly at the expense of exports. Currently, the requirements for the quality of liquid plasters for the treatment of wounds are not unified. Still, more attention is paid to drugs with higher quality requirements in the pharmaceutical market than to representatives of a similar pharmaceutical line (17). To understand the prospects and directions of development in the manufacture and sale of soft medicinal forms in the form of a patch, it is worth comparing the requirements for quality control of these medicinal products in Ukraine and countries with a high level of development of the health care and pharmaceutical industries.

The EU was chosen for this, considering the appropriate level of European quality standards and status (13). Ukraine was selected since it is a candidate for joining this organization with the expansion of these standards, in particular, to the pharmaceutical industry of the state (7). Great Britain, as a European country that is not a member of the EU, has a high standard of living for its citizens and corresponding quality standards in health care and pharmaceuticals (14, 18). Japan was included, considering the large number of innovative developments in the creation of medicinal products and the corresponding level of their quality control (15,19).

In the Ukrainian Scientific Pharmacopoeia Center for the Quality of Medicines, liquid plasters are combined in one group with other medicinal products belonging to soft dosage forms; therefore, when comparing the requirements in the pharmacopoeial articles, the quality indicator of the entire group of preparations will be considered, and attention will be focused on those of them that are the most important for quality control of the researched product. Classification of liquid plasters and general quality indicators of soft dosage forms are given in Table 1.

Having familiarized oneself with the pharmacopoeial articles of Ukraine, the EU, Great Britain, and Japan, it is worth paying attention to the differences between the approaches to the classification of soft dosage forms. So, the Ukrainian Scientific Pharmacopoeia Center for the Quality of Medicines (7), the Council of Europe (13), and the Medicines and Healthcare Products Regulatory Agency (14) have a separate article for consideration of the characteristics and requirements for soft dosage forms for dermal application. In the Ministry of Health, Labour and Welfare (15), drugs are grouped according

Table 1. Classification of liquid plasters and general indicators of the quality of soft dosage forms

Pharmacopoeia	The name of the pharmacopoeial article	The name of the medicinal product, according to the pharmacopoeial article	Definition of the medicinal product according to the pharmacopoeial article	Quality indicators of soft dosage forms
State Pharmacopoeia of Ukraine	Soft medicinal means for skin application Semisolid preparations for cutaneous application	Medicinal and skin plasters	Soft dosage forms intended for local action, transdermal delivery of active substances, or softening or protective action	description; identification (active pharmaceutical ingredients, antimicrobial preservatives, active substances); uniformity of dosage units; particle size; pH; acid and peroxide value; viscosity; release of active pharmaceutical ingredients; quantitative definition; microbiological purity/ sterility; tightness of the container.
European Pharmacopoeia				
British Pharmacopoeia	Topical semi-solid preparations			
Japanese Pharmacopoeia	Monographs for Preparations. (Preparations for Cutaneous Application	Plasters	Plasters are dosage forms intended for attachment to the skin	

Source: compiled by the author based on (7;13-15).

to use. Therefore, soft dosage forms are not combined into a separate group but are considered along with solid forms as separate medicinal products. Quality indicators of soft dosage forms in the Ukrainian Scientific Pharmacopoeia Center for the Quality of Medicines (7), Council of Europe (13), and Medicines and Healthcare Products Regulatory Agency (14) turned out to be the same. In the Ministry of Health, Labour and Welfare (15) indicators of "homogeneity of dosage units", "acid and peroxide value", "release of active pharmacological ingredients", were not declared. The most important indicators for quality control of liquid plasters are "sterility", as they are in contact with the affected surface, and "release of active pharmacological ingredients", as the therapeutic effect of the medicinal product depends on it. In the Ukrainian Scientific Pharmacopoeia Center for the Quality of Medicines, this indicator is controlled according to the method of the "Dissolution" test (7).

The comparisons showed that the requirements for groups of soft dosage forms, including liquid plasters, do not differ in European countries. Instead, the pharmacopeia of Japan has differences in structure and discrepancies in the quality indicators of medicines compared to other pharmacopeias. This can be explained by the fact that, by grouping soft and hard dosage forms according to application, those indicators that ensure the properties of soft dosage forms were not considered. It can also be explained by the difference in pharmaceutical markets, which, although they have general trends, are subject to the influence of national and regional characteristics. A comparison of the requirements for liquid plasters in Ukraine, the EU, Great Britain, and Japan based on their pharmacopeia articles showed that the Ukrainian Scientific Pharmacopoeia Center for the Quality of Medicines requirements are at the level of other European countries but have certain differences with the Japanese pharmacopeia. Thus, to improve the interaction between the main pharmaceutical markets of the world, it can be considered appropriate to unify the system that ensures quality control of medicinal products. At the same time, the same level of requirements for drugs combined in the group of soft dosage forms in the pharmaceutical industry of Ukraine, the EU, and Great Britain provide prospects for development. It expands directions for the creation and promotion of drugs of this group on the European market.

To create a new drug, the necessary conditions for the effective therapeutic effect of APIs are the creation of a drug of appropriate quality with a given therapeutic activity, bioavailability (rate and degree of absorption) of APIs, and defined routes of entry into the body. Changing the way APIs enter the body makes it possible to improve the therapeutic effect by prolonging the therapeutic effect of the active and auxiliary components of the product, ensuring targeted delivery, and reducing the negative impact on other systems and organs. Studying in this research the technological aspects of developing a liquid patch for treating wounds, it is important to pay attention to those characteristics of this dosage form, thanks to which an increase in the effectiveness of the therapeutic agent and the convenience of its use is ensured. Since the therapeutic effect of the liquid patch occurs directly in contact with the skin, it is worth studying the structure of the skin and the process of its healing in detail to understand the mechanism of action of this medicinal product and the advantages associated with the updated medicinal form.

Peculiarities of skin structure and wound healing process

The skin is the largest organ in the human body; its weight is approximately 7 % of the body weight, and the area varies from 1.5 to 2 m^2 (20). It consists of three layers: epidermis (upper horny layer), dermis and hypodermis. In different parts of the body, the epidermis and the dermis have various thicknesses of 0.5-5 mm, and the thickness of the hypodermis can reach 10 cm (21). The function of protection explains the difference in the thickness of the upper layers of the skin – areas of the body that are more affected by environmental factors, respectively, need more protection (areas of the palms and feet). The skin contains blood and lymphatic vessels, nerve endings, sweat and sebaceous glands, receptors, hair follicles, Merkel discs, Pacini corpuscles, and Meissner corpuscles (22,23). Protecting dangerous microflora entering the body is due to the density of the stratum corneum and the

acidic environment on the skin's surface, which is pH 5-6.5 (24).

Damage to the integrity of the skin is dangerous for the entire body and can lead to an infectious disease of varying degrees of severity. To prevent this process, the treatment should include disinfection of the injured surface and using drugs to heal the wound. When developing these products, the physicochemical features of the active substance are considered, which ensures its penetration to the necessary layers of the skin, taking into account the resistance of each of them. Penetration of substances into the skin is carried out through transepidermal (through the stratum corneum of the epidermis without damage to its integrity (25)), transfollicular (through hair follicles (26)), and transglandular ways (through the ducts of the sweat glands (27)).

The main part of soft drugs penetrates the skin using the transepidermal route. In this case, the active substance can penetrate both extracellularly – passing between cells, and intracellularly – passing through cells. Hydrophilic, emulsifying, and absorbent substances show the best absorption capacity with the help of soft dosage forms (28-30). Wound healing is a natural process in the human body, even without external intervention. Still, without providing the necessary medical measures and taking into account the type and size of the injury, this process can be complicated under the influence of both external and internal factors and lead to negative consequences that may occur at each stage of this process. Healing consists of four stages: homeostasis, inflammation, regeneration, and reorganization (31). The homeostasis stage lasts for several minutes and combines the processes of coagulation with thrombus formation and lysis of blood clots. Mechanically, the process of homeostasis consists of blocking the damaged site with platelets that collect and stick together, forming the primary occlusion of the wound (32). Secondary blockage occurs due to the formation of fibrin threads.

The inflammation stage lasts from the first to the fifth day, including vascular changes and wound cleaning from necrotic tissues (33,34). In the period of vascular changes, there is a violation of the outflow of blood and lymph provoked by damage to the vessels. Visually, this process can be determined by the development of tissue swelling, which characterizes the stage of inflammation. This is due to a decrease in perfusion, which reduces the level of tissue oxygenation on the wound's surface, which in turn provokes a violation of carbohydrate and protein metabolism. Ions are released from the destroyed cellular proteins, which ensure an increase in osmotic pressure, which leads to water retention and the development of edema (35). Formed blood elements and enzymes clean the wound from necrotic tissues (36). From the first day, this function is performed by neutrophils appearing in the exudate and tissues around the wound, and from the second to the third day, by lymphocytes and macrophages (37,38). At the same time, lymphocytes help the body implement an immune response, which is very important since, at this stage, there are risks of complications during the healing process.

The regeneration stage lasts from the sixth to the fourteenth day. During this period, the main mass of collagen is formed and synthesized with the participation of fibroblasts, which migrate to the wound area after the number of neutrophils in it decreases. Simultaneously with this process, the damaged channels of blood and lymphatic vessels are restored, which contributes to the extinguishing of the inflammatory process and the disappearance of edema (39). The fourth stage of healing, – reorganization, begins on the fifteenth day and can last up to six months. All processes, except those that reduce the formed scar's strengthening, decrease their activity during this period (40). Cross-links are formed between the collagen fibers, reducing the scar's size and increasing its strength. At the same time, slowing down the formation of new blood vessels contributes to the lightening of scar tissue. In the absence of complications at this stage, by the end of the fourth month, the strength of the formed scar is 90 % (41).

Factors that negatively affect the wound healing process include the age of the person, lack of nutrients in the diet, metabolic disorders, diseases that reduce the body's ability to regenerate, bad habits, and drying of the wound surface (42). Since the peculiarities of the skin structure and the routes of entry formed the requirements for the physicochemical characteristics of the active substance of the liquid patch, the considered

material regarding the process of its healing also formed the requirements for the dosage form, which is best able to ensure a comfortable and unhindered delivery of the same substance, eliminating factors capable of worsening the flow of this process. Therefore, in the technological development of a liquid patch, it is necessary to develop such a tool that can ensure the possibility of keeping the wound moist, avoiding its drying, thereby accelerating healing. Thus, during the technological development of a liquid plaster for the treatment of wounds, it is necessary to consider the peculiarities of the structure and function of the skin and the physicochemical properties of the main and auxiliary substances.

Today there are many cosmeceuticals dermatoprotective agents, the main task of which is to protect the skin from pollution, sunburn, etc. Such products have a mild protective effect but are applied exclusively to intact skin. As for medical liquid plasters, which can also be classified as dermatoprotectors, their main action is aimed at protecting the damaged area of the skin from the effects of irritating agents by creating a transparent film on the surface of the wound. Such products do not have a cosmetic effect; their main function is protection and wound healing. Therefore, developing new medicines that combine combinations of APIs and auxiliary substances with a pronounced therapeutic and protective effect that promotes wound healing and contain substances with antimicrobial properties, in particular natural components, is relevant.

The main and auxiliary substances included in the composition of the liquid patch

As defined in the Pharmaceutical Encyclopedia, liquid plasters are volatile liquids of natural or synthetic substances, which, after evaporation of the solvent, form a strong elastic film on the skin (43). Elastic films that do not contain APIs are called skin adhesives. Their function is limited to fixing bandages. Films containing APIs perform a corresponding therapeutic effect in addition to the fixing effect. Actually, such liquids are called liquid plasters (6). Liquid plaster is characterized by the same indicators as other medicinal products, namely composition, dosage form, pharmacotherapeutic group, pharmacodynamic and pharmacokinetic properties, clinical characteristics, and application features.

Depending on the type of film, former liquid plasters are divided into collagen and resin. Currently, only resin skin adhesives are available on the domestic pharmaceutical market. Skin glue, with the trade name BF-6, produced by OJSC Lubnyfarm, is presented in Ukraine's market. Leather glue BF-6 is an alcoholic solution of a modification of phenol-formaldehyde resin, polyvinyl butyral, and rosin, plasticized with a plasticizer. BF-6 glue has a wound-healing and antiseptic effect. It is used as an insulator to promote the healing of small skin wounds due to the formation of an insulating film on their surface. The latter is elastic and resistant to mechanical and chemical influences. When covering the root of a tooth with Glue BF-6, conditions are created to isolate the microflora of small root canals from the products of tissue destruction. BF-6 glue is used for treating microtrauma – wounds, scratches, cuts, and other minor skin injuries, as well as for covering the root of a tooth during surgical treatment of periradicular foci of infection: cysts and granulomas.

Currently, the development of skin adhesives, which include APIs, is promising, however, the determination of one of the important indicators, namely the release of the active substance, is a necessary requirement for the standardization of this medicinal product. The composition of liquid plasters can include extracts from medicinal plant raw materials and chemotherapeutic drugs. Especially relevant is the use of liquid plasters in dentistry to treat periodontal disease, including horsetail grass extract liquid. Dental plasters in their aggregate form are liquid plaster, which, after applied to the focus of inflammation, quickly lose the solvent and leave a thin elastic film.

The polymer base is a significant factor that ensures the effectiveness of biologically active substances in glues. The basis of these medicines is presented in the form of a film-forming system. The film-forming system comprises a film-forming substance, its solvent, and a plasticizer (44). Active pharmaceutical ingredients perform a therapeutic effect and are the active substance or substances in the medicinal product. The same active pharmaceutical

ingredients can be used, both, in a liquid patch and in its classical form on a substrate. Plant-based substances (extracts of medicinal plants, tinctures, etc.) and chemically synthesized substances (non-steroidal anti-inflammatory drugs, anesthetics, antibiotics) can be used as such ingredients. Changing the form of the drug from a traditional to a soft form was achieved thanks to the development of a film-forming system, which became a replacement for a substrate on a paper, canvas, or other basis.

In the development of the film-forming substance, components of natural (vegetable resins) and synthetic origin (acrylic polymers, cellulose derivatives) are used. Modern pharmacology pays more and more attention to the use of polymers due to their properties and ease of use (45). In the development of film-forming substances, polymers are used separately or combined to ensure the necessary characteristics of the finished drug. Their main advantage is forming a stable, flexible, thin, transparent film. The main polymer film formers include carbopol (polyacrylate), chitosan (poly-D-glucosamine), hydroxypropyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, ethyl cellulose, hydroxypropyl methylcellulose, acrylate copolymer, cross-linked polymer layer XPL, copolymer polymethacrylate, silicones (46-48).

Carbopol (polyacrylate) has a good film-forming ability, belongs to water-soluble polymers, and is sensitive to pH. Chitosan (poly-D-glucosamine) provides increased penetration of the drug into the appropriate layers of the skin, has a high film-forming ability, is water-soluble at pH<7, and controls drug release. Hydroxypropyl cellulose is a polymer with high film-forming ability, water-soluble, and pH-insensitive. Polyvinylpyrrolidone has adhesive and binding properties, high hygroscopicity and biocompatibility, provides increased bioavailability, and is water-soluble. Polyvinyl alcohol has good film-forming and adhesive properties, is characterized by non-toxicity and biocompatibility, and is a water-soluble polymer. Its low hydrophilicity makes forming a hard but not sufficiently elastic film possible. Biocompatibility is a crucial consideration in the development of liquid plasters. It describes a substance's capacity to carry out its intended purpose in a way that produces the most advantageous cellular or tissue response in that particular circumstance while avoiding any unfavorable local or systemic effects on the patient receiving the therapy. Biocompatibility is important for liquid plasters since the skin and wound surfaces are in direct and extended contact with these products. The surrounding tissues shouldn't be harmed, allergic, or irritated by a biocompatible liquid plaster. It should promote the body's natural healing process for wounds without adversely affecting tissue regeneration or cellular processes. The selection of polymers, solvents, plasticizers, and active substances in the composition of liquid plasters determines their biocompatibility.

Ethylcellulose has good film-forming properties, which make it possible to form films of high strength. The polymer is hypoallergenic, non-toxic, and non-irritating. According to the solubility classification, it is insoluble in water. Hydroxypropyl methylcellulose ensures the formation of a uniform, non-greasy, light transparent film with a good texture. Significant interaction with other ingredients is not observed. The substance has surface-active properties – it adsorbs water, provides easy dispersion, and in the occlusive state, when applied to the skin, it provides lubrication and a comfortable feeling. Acrylate the copolymer ensures the formation of a strong, abrasion-resistant, breathable film. A cross-linked XPL polymer layer makes forming an elastic film with high adhesiveness possible. Copolymer polymethacrylate ensures the formation of an elastic, transparent, self-adhesive film with good skin adhesion. Silicones allow the creation of a strong and, at the same time, vapour-permeable film.

Solvents in film-forming systems ensure the active substance's dissolution and penetration into the appropriate skin layer. The general requirements for solvents are as follows: the formation of a polymer film must occur within less than one minute after applying the drug; therefore, under the influence of the temperature of the skin surface, the solvent must evaporate evenly within the specified time to ensure the formation of a homogeneous film. The requirements for solvents from the side of interaction with the skin consist of ensuring compatibility and the absence

of an irritating effect in the evaporation process, and from the side of the film-forming substance – ensuring good dispersion or dissolution of this substance in the solvent. The following substances meet these requirements: glycols (propylene glycols, polyethylene glycols), alcohols (ethanol, butanol, isopropanol, benzyl alcohol, lanolin alcohols, fatty alcohols), ethyl acetate, isopropyl myristate, oleic acid.

Plasticizers are used to solve the problem of the fragility of polymer films, to ensure the reliability of their adhesion to the skin's surface, and to improve the covering capacity on hard-to-reach areas of the skin. The main requirement for substances used as plasticizers is low skin permeability and compatibility with film-forming substances, which ensures the ability to penetrate between the polymer chains of this substance, weakening the intermolecular bonds between them and thus increasing the flexibility and strength of the formed film. The study of plasticizers showed that their optimal concentration from the total volume of the dry weight of the film is from 5 % to 20 % (49). According to these requirements, the following substances are used as plasticizers: glycerine, sorbitol, dibutyl phthalate, triethyl citrate, polyethylene glycol, and propylene glycol (50).

Liquid plasters belong to the soft medicinal form and are viscous liquids that form an elastic, strong film after application to the skin (51,52). According to the pharmacotherapeutic group, liquid plasters belong to anti-inflammatory, anesthetic drugs for local use. The pharmacodynamics of the liquid patch has the following mechanism: with local application of the drug, the active substance penetrates through the skin's surface, reaching the desired layer, and has a pain-relieving, anti-inflammatory effect, reducing swelling. The pharmacokinetics of this medicinal product consists in maintaining the necessary concentration of the active substance in the relevant tissues of the body due to constant penetration from the patch, regardless of the time of day, the activity of the person using the drug, and other external factors. The mechanism of metabolism and removal of the active substance during local application is determined by the nature of the given substance. It must correspond to how it was during other forms of medicinal product application.

Clinical characteristics of the liquid patch include indications and contraindications for use, the level of interaction with other drugs, and other types of interactions. Indications for the use of liquid plasters are local treatment of wounds. Contraindications may be hypersensitivity to the active substance of the medicinal product or the presence in the anamnesis of negative consequences caused by taking drugs that contain the same active substance as the liquid patch. The liquid plaster's medicinal form limits the interaction of its active substance with other medicinal products. Features of using a liquid plaster are prevention of contact with mucous membranes and eyes, control of the healing process (in case of worsening of its condition, consult a doctor), control of the condition of the skin in the wound area and around it (in case of the appearance of rashes or other skin conditions reactions should stop using the drug). The use of this medicinal product during pregnancy or breastfeeding has certain features that depend on the active substance in its composition. The negative effect may be minimal or absent when applying a liquid patch while driving a motor vehicle or other mechanical means.

Comparing the characteristics of the liquid patch and the patch on the substrate, the difference was found in the composition of the drug and its dosage form. Still, the clinical characteristics and features of using both drugs did not differ. No difference was found in the pharmacodynamics of both dosage forms, but significant differences in pharmacokinetics generally indicated the advantages of the pharmacological properties of liquid plasters. In this way, a number of advantages of soft dosage forms in the form of a patch were revealed, which include the provision of prolonged release of the active substance, an increase in the concentration of the active substance several times after the evaporation of the solvent, which ensures better penetration into the layers of the skin; providing an infectious barrier thanks to the formed film; storing the wound in a moist environment; absence of discomfort and pain during application; ease of use, which makes it possible to close wounds of various sizes and shapes, especially when applied to hard-to-reach areas or areas of the body that are difficult to bend (perineum, nail corner, bend of the leg, hand, finger).

The mechanism of the therapeutic effect of liquid plasters

The main technological aspects of developing a liquid plaster for treating wounds were based on the need to improve the characteristics of the traditional medicinal form of the plaster and improve the therapeutic effect of the active substance in its composition. Thus, based on the anatomical features of the skin structure, the wound healing process, and the requirements for the constituent ingredients of the medicinal product, which are formed based on its clinical characteristics, it is possible to form a mechanism of film formation and penetration of the active substance into the corresponding layers of the skin. This mechanism is a cascade of processes that are launched immediately after the use of the medicinal product. These processes are ensured by the properties of the substances that are part of the film-forming system and begin to manifest when they come into contact with the skin. In this way, the light components of the solvent evaporate under the influence of the temperature of the skin surface and leave a light, strong, and plastic film on its surface, the characteristics of which are provided by the properties of the film-forming substance and the plasticizer. Under the influence of these processes, the concentration of the active substance increases, which leads to an increase in its flow through the skin due to an increase in the level of thermodynamic activity. According to the requirements for film-forming systems, they do not impact the skin barrier, making it possible to avoid side effects and irritation. At the same time, the strong contact of the film with the skin prolongs the effect of the active substance, which speeds up the wound healing process (53). The considered mechanism of film formation and penetration of the active substance made it possible to obtain a new form of medicine for the treatment of wounds for local use, which has advantages in characteristics compared to a traditional plaster on a canvas, paper, polymer, or other type of substrate.

Their adhesive qualities significantly influence the efficacy and user satisfaction of liquid plasters. Liquid plaster adherence poses distinct obstacles for different skin types. Excess sebum on oily skin can prevent a stable film from forming, which could lower adhesion and jeopardize the wound barrier. On the other hand, the absence of natural moisture on dry skin may interfere with the liquid plaster's initial adhesion and distribution. The adhesion characteristics of liquid plasters are also greatly influenced by physiological and environmental conditions. Sweating is a common problem in wound care that may jeopardize the liquid plaster film's integrity. Sweat hydration may accelerate the film's deterioration or lessen its stickiness to the skin. Likewise, joints and the hands are examples of body parts constantly moving and flexing, making it difficult to maintain continuous adhesion. It must be sufficiently flexible to continue acting as a protective barrier and allowing the liquid plaster to move with the skin without peeling or breaking.

Innovative modern plasters

The main advantages of plasters are their medicinal form, which, on the one hand, allows isolating the wound from the influence of environmental factors and, on the other – ensures the controlled delivery of the active substance to the wound surface through close contact with the skin. Thus, these properties were used in developing a hydrogel skin patch to treat chronic wounds, including diabetic foot ulcers. The advantage of the hydrogel patch is the ability to provide a long-term release of the active substance and a controlled pH level on the wound surface. The mechanism of action of this patch, when applied to a diabetic foot ulcer, can be described as follows: in a bacterially infected chronic wound, in contrast to the state of integrity of the skin, an alkaline environment is maintained, which activates the dosed release of antibiotics from the hydrogel. This process continues until the pH of the wound reaches the level of an acidic environment, which allows the natural healing process to continue (54).

Using the advantages of liquid plasters in the healing of wounds and burns, modern developers are actively working on the possibility of increasing the effectiveness of treating other diseases, using the possibility of this dosage form for non-invasive administration of drugs. The use of transdermal patches of nanocomposite polymers makes it possible to release those cells of the active substance that contain biomolecules and micro-RNAs useful for treating a specific disease (55). Such material properties made it

possible to develop a collagen-based hydrogel patch to treat myocardial infarction (56). The therapeutic effect in this case is provided by the stable release of the active substance from the implanted hydrogel patch for 21 days, significantly reducing the size of heart muscle damage, apoptosis, and hypertrophy.

Liquid plaster development has witnessed notable technological developments in recent years, utilizing state-of-the-art innovations to improve its usefulness and efficacy. In this area, nanotechnology has changed everything by creating liquid plasters filled with nanoparticles with better antibacterial qualities and controlled drug release. Silver nanoparticles, for example, have been added to liquid plaster formulations to offer strong antibacterial properties without running the danger of antibiotic resistance. With the introduction of stimuli-responsive polymers that may alter their characteristics in reaction to environmental cues like temperature, pH, or certain biomarkers, smart materials represent another frontier in the evolution of liquid plaster. These intelligent liquid plasters may adjust to the environment around the wound, promoting healing or releasing medication only when necessary. Moreover, developments in polymer science have produced liquid plasters that may self-heal and restore tiny tears in the protective layer, extending the duration of wound healing.

Close contact with the skin and the therapeutic effect allows the plaster to act as a tool for monitoring physical health. Therefore, a promising direction for using plasters is developing biomedical means for non-invasive control of human physiological indicators in real-time. Built-in biosensors record physiological indicators in these patches. The biosensor materials are polystyrene sulfonate, graphene, and carbon nanotubes, and the substrate materials are polyurethane and silicone. The main indicators that can be monitored thanks to patches with biosensors are motor activity, energy level, heart rate, muscle response, skin moisture level, skin-galvanic response, electroencephalogram, electro-oculographic signal, body temperature, volume, and composition of sweat, the composition of tears (57). It is worth noting that the most informative indicators are the content and volume of secretions. Vegetative and metabolic disorders, nerve damage, chronic stress, and diabetes can be detected by the composition of sweat (58, 59). Analysis of the composition of tears makes it possible to determine the presence of such diseases as ocular rosacea, dry eyes, glaucoma, conjunctivitis, lacrimal gland dysfunction, allergic conjunctivitis, blepharitis, meibomian gland disease, pterygium, Sjorgen's syndrome, diabetes, diabetic retinopathy, autoimmune thyroid disease, herpes simplex virus, cancer, AIDS (60,61). The storage of information obtained from continuous monitoring of the physiological parameters of the body can be carried out using cloud service applications on smartphones. The analysis of the received data can be carried out using developed algorithms of machine learning, the Big Data method, artificial intelligence, or a medical representative that receives sensor information from the patient (62).

The painlessness, convenience, and simplicity of pharmaceutical skin plasters allow for the constant expansion of directions for their use. The joint efforts of the biochemical and medical industries make it possible to improve the patch material, improve its characteristics, increase the effectiveness of the therapeutic effect, and control the body's physiological parameters.

Discussion of prospects and directions in the development of liquid plasters for the treatment of wounds

Considering the prospects for developing certain medicinal products in Ukraine, it is worth familiarizing oneself with the development of its pharmaceutical industry as a whole. Shandrivska and Tsvetkovska considered this issue from the marketing and pharmaceutical component side and published the results obtained during the study of the pharmaceutical market of Ukraine (63). The scientists studied in detail the dynamics of its development during the spread of the COVID-19 pandemic, analyzed the competitive positions between pharmaceutical market participants, and assessed the concentration of this market using statistical methods specific to market calculations. It was established that the Ukrainian market of pharmaceutical products as of 2022 formed about 1 % of the country's Gross domestic product (GDP) and developed with a significant increase. The impact of the pandemic on the structure

of the Ukrainian pharmaceutical market was expressed in increasing sales of antimicrobials, complicating the situation on domestic and foreign markets, complicating export-import operations due to logistical restrictions between countries, aggravating the competitive situation between the target markets of pharmaceutical products. The conducted calculations made it possible to determine the companies that occupied the highest positions in the pharmaceutical market of Ukraine, among them: JSC "Farmak", Corporation "Arterium", PJSC "Darnytsia". It is possible to agree with the results of the work carried out, as they were based on objective data obtained thanks to the monitoring of the Ukrainian pharmaceutical market, but the information cannot be considered relevant at the moment since its results were obtained before the full-scale war in Ukraine. Therefore significant changes were not taken into account, which took place in particular in the state's pharmaceutical industry.

The most acute problems faced by the industry after a full-scale invasion: a shortage of imported drugs due to disruptions in the logistics of overseas supplies, the loss of about 15 % of product consumers due to the departure abroad of 6.5 million Ukrainians, which included mainly women, children, and the elderly (64-66). Currently, the situation with the provision of medicines has been stabilized thanks to the establishment of the normal working regime of Ukrainian pharmaceutical manufacturers, the restoration of foreign supplies, government steps related to operational decisions on granting the necessary permits to simplify the import of medicines from abroad and their manufacture on the territory of Ukraine, the receipt of humanitarian aid, development of volunteer and charitable activities. Currently, for the development of the industry, it is important to form and increase export opportunities; this can be helped by the support of the leaders of the world pharmaceutical market due to the removal of several regulatory restrictions in this industry. Since the world pharmaceutical leaders are the United States of America, the EU and Japan, the states that support Ukraine in the military, social and economic spheres, it is worth hoping for the partnership relations of these countries in the direction of the development of the external pharmaceutical market of Ukraine.

Liquid plasters have many benefits for treating wounds, but it's vital to consider how they may affect the environment. Synthetic polymers and solvents are used to create liquid plasters, which may increase carbon emissions and resource depletion. Waste management systems may also face difficulties disposing of leftover products and used liquid plaster packaging. In contrast to conventional cloth bandages, which are frequently biodegradable, the film that liquid plasters leave behind could linger in the environment for longer. However, some of these effects might be mitigated because less material is used than typical bandages.

When considering the world pharmaceutical market situation, it is worth paying attention to research conducted in countries that occupy leading positions in this field. In the work of Krausz et al., an analysis of the changes in the North American drug markets and the challenges they pose to the healthcare system was carried out (67). The authors consider the general problems associated with the change in the pharmaceutical markets of the region, which consist of the shift in the market of narcotic drugs in the direction of powerful synthetic opioids, which provoke the development of a public health crisis. As a solution to the problem, the authors propose to develop and ensure effective management of health care with the unification of the necessary state and public structures and the involvement of the necessary resources. At the same time, using the experience of the COVID-19 pandemic will help to avoid mistakes and choose the right decisions, which consist of the use of innovative technologies, attracting investments in improving security measures, and organizing coordination of the directions of clinical activity development. The authors raised the most acute issues for the North American region in the field of production and sale of medicinal products, but a general market study, in particular soft medicinal products for dermal application, was not carried out; therefore, they agree with the conclusions of the authors and use the information obtained as a comparison of the pharmaceutical markets of Ukraine and this region is currently impossible.

Laurano et al. considered an assortment of products for application to wounds (68). In the study, all forms of topical agents for use on wound surfaces were given, and special attention was

paid to the study of wound dressings and ways of their improvement through electroforming and 3D printing methods. Information on the ways of developing and improving liquid plasters for the treatment of wounds was not considered, so one can only partially agree with the results of the study. The reviewed publications showed that information on the use of soft medicinal forms in the form of a liquid plaster for the treatment of wounds in foreign sources is not covered in detail, which may be a sign of the limited use of these drugs in the world pharmaceutical markets (63, 64). However, their advantages indicate significant prospects and directions for further development both in the domestic pharmaceutical market of Ukraine and as an export product. In addition, the availability of raw materials, proven manufacturing technology, and compliance with the requirements for the quality of medicinal products to the standards of the European and Japanese pharmacopeia will make the export process economically profitable for both sides of the market.

CONCLUSIONS

A comparative analysis of the requirements of the pharmacopeia articles for quality control of soft dosage forms in the form of patches in Ukraine, the EU, Great Britain, and Japan was conducted. Comparison of State Requirements Pharmacopoeia of Ukraine, European Pharmacopoeia, British Pharmacopoeia, and Japanese Pharmacopoeia for soft dosage forms, which group includes liquid plasters, revealed certain differences in approaches to the classification of these drugs and discrepancies in their quality control indicators. Thus, a difference in classification was found between the approaches of the European pharmacopeias and the pharmacopeia of Japan, which the regional characteristics of the pharmaceutical markets of the studied countries can explain. In the Ukrainian Scientific Pharmacopoeia Center for the Quality of Medicines, European Pharmacopoeia, and British Pharmacopoeia, quality indicators of soft dosage forms were the same. In the Japanese Pharmacopoeia, some indicators included in the list of requirements of pharmacopoeias of other countries were not declared. Among the list of all indicators of the quality of soft dosage forms, the most important for liquid plasters is the indicator of "sterility," which was included in the list of all studied pharmacopeias, and "release of active pharmacological ingredients," absent in Japanese Pharmacopoeia. A comparison of the requirements for quality control of soft dosage forms, in particular liquid plasters, showed that the requirements of the Ukrainian Scientific Pharmacopoeia Center for the Quality of Medicines are at the level of other European countries therefore this group of medicines can be considered as goods for export to the European pharmaceutical market. However, to implement this recommendation, it is necessary to conduct an additional study of the range of liquid plasters and compare them with similar European ones.

The peculiarities of the skin structure and the wound-healing process were analyzed. The conducted literature search for scientific information regarding the wound healing process made it possible to formulate the requirements for the dosage form, namely: prolonged release of APIs; the formation of a film that serves as a barrier to reinfection and prevents the transfer of mycelial cells; preservation of the wound in a moist environment; strengthening of re-epithelialization, synthesis of collagen, which leads to reduction of wound infection. The main characteristics of the liquid plaster (composition, dosage form, pharmacotherapeutic group, pharmacodynamic and pharmacokinetic properties, clinical characteristics, and application features) were considered as its advantages over traditional plasters. The role of APIs with antimicrobial properties of natural origin, a combination of auxiliary substances capable of forming a thin transparent impermeable film (Film former, solvent, and plasticizer) was studied. The types, functions, and requirements for the components of the film-forming system were studied in detail, as the quality of the film-formation process and the subsequent release of active pharmaceutical ingredients depend on them. The perspectives of using liquid plasters (skin adhesives), features of their technology, and quality control methods were summarized.

Future research should explore novel biocompatible and biodegradable polymers that could lead to more environmentally friendly and skin-compatible formulations. More research

is required on the long-term impacts of these treatments on skin health and wound healing processes to guarantee the safety and effectiveness of liquid plasters over an extended length of time. Additionally, research into improving the adhesion properties of liquid plasters across various skin types and environmental conditions could enhance their reliability and user satisfaction.

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