Transdermal Pharmacotherapy: Traditions and Innovations

ABSTRACT
The review is focused on the development questions and transdermal medicines usage. The advantages and limitations for transdermal drug administration are presented. The analysis of 70 scientific sources is performed. The morphological and functional structure of the skin as a factor of transdermal drug delivery into the body is described. The review provides information on transdermal therapeutic systems (advantages, disadvantages, structure, technology, scope). The possibility of using transdermal therapeutic systems for the vaccination and local anesthesia, treatment of arthritis, Alzheimer’s disease, contact dermatitis, burn wounds, infectious diseases, osteoporosis, oncology and other pathologies is discussed.

KEYWORDS transdermal therapeutic systems, pharmacotherapy, medicines

INTRODUCTION
The development and implementation of the innovative dosage forms are priority for the pharmaceutical industry. Over the last decade, about 25% of the world sales of drugs are taken by drugs with an improved drug delivery system1–4.

Considerable attention is paid to research and development of drugs of transdermal action5–8. This is due to the fact that the transdermal dosage form of their delivery into the body with a therapeutic purpose has proved to be the most effective for many of the drugs that have already been developed and currently under development. This is determined by the ability of drug molecules to penetrate the epidermal barrier, mainly through the keratinizing part of the epidermis, which contains lipids in its structure1–3.

MORPHOLOGICAL AND FUNCTIONAL STRUCTURE OF THE SKIN AS REGULATING FACTOR OF TRANSDERMAL ADMINISTRATION OF DRUGS INTO THE BODY
The ability of drugs assimilation through the skin is due to its physiological and structural characteristics9,10. The epidermis consists of a multilayer flat epithelium and it is divided into two zones, which sharply differ biologically. The zone including basal and spinous layers is oxybiotic, and the zone consisting of granular, shiny and horny layers is anoxibiotic, perform different functions. Intensive oxidative processes are carried out in the oxybiotic zone, and these processes are enzymatic in nature and not so intense in the anoxibiotic. There is little oxygen in the cells of the granular layer, no Golgi apparatus; the number of mitochondria that contain the enzymes of the respiratory chain is reduced. However, there is DNA in the nuclei of the granular cells layer, which indicates their functional activity. The surface layer of the epidermis smoothly passes into the subsequent connective tissue layer of the skin—dermis, hypodermis and fatty tissue1,3,11.

The skin vessels form up to four layers of arterial and venousplexuses, the capillaries of which extend into the surface layers. An extensive vascular network provides fast penetration of the medicines applied to the skin in the total blood flow. The speed of blood circulation in the skin is provided as a regulatory contraction of arteriolar spinhecers, and the presence of arteriovenous anastomoses ranging in papillar plexus. The skin is rich in lymphatic vessels. They form a dense plexus of the lymphatic capillaries in the papillary layer, the blind processes of which are located more deeply...
in the epidermis in comparison with the blood vessels. Lymphatic vessels are well defined at the border with the hypodermis and are often provided with valves. Depending on the temperature of the environment, the vessels of the pantyplete plexus are open or close, regulating the blood circulation\(^1\).

Lipids, soluble in them substances or substances that dissolve lipoids (ether, alcohol, essential oils, chloroform, resorcinol, etc.) are much easier absorbed through the skin. Skin damage, as well as infection, compressing are greatly facilitated the absorption of many substances\(^{12-14}\).

Skin as a blood pool plays an important role. Normally, a large number of cutaneous vessels are in a semi-reduced state. Only the vessels of the dermis can hold 1 l of blood in case of their expansion. Arteriovenous anastomoses are important in the regulation of blood circulation\(^9,15\).

There are numerous free nerve endings in the skin. The narrowing of the skin vessels is caused by the action of sympathetic vasoconstrictor nerves—vasoconstrictors. Parasympathetic vasodilator nerves are not found in the skin. It is possible to participate in the expansion of vessels transferring excitation from the receptor to the effectors in the vascular wall by the type of so-called axon reflexes. The skin contains a large number of receptors, the sum of which is the skin analyzer’s peripheral part. The following types of skin sensitivity are distinguished: thermal, cold, tactile, and painful. The skin is an extensive reflexogenic system, provided with numerous and diverse receptors, its function is important in the vital activity of the organism. There is a correlation of the skin condition with the digestive apparatus, skin-respiratory, skin-cardiovascular and other skin-visceral reflexes that affect the changes in the brain biocurrents\(^7\).

The skin plays an essential role in the metabolism of the body due to the huge surface and considerable mass (the only epidermis mass and dermis is approximately equal to the mass of blood), the presence of a powerful peripheral circulatory and lymphatic network. Skin is an extensive tissue environment involved in the body’s metabolism regulation, most often in the form of a pool of large reserve capacity. These or other products of tissue and general metabolism under normal conditions can functionally be delayed, and it is not accompanied by any disorder of skin functions\(^8\).

Skin is an important organ that takes an active part in the processes of water and mineral metabolism. The content of potassium and calcium in normal skin is much higher than in serum (10–40 mmol/l of potassium and 5–11.3 mmol/l of calcium). Moreover, the skin shows a wider range of fluctuations in the level of potassium and calcium than in blood serum\(^9,15\). All physiological properties of the skin should be taken into account when introducing drugs into the body.

**TRANSDERMAL DELIVERY OF MEDICINES**

The mechanism of penetration of exogenous substances through the skin is a complex and multiform process. Medicinal substances penetrate the body through the keratin layer of the skin by absorption, partly through the hair follicles and sebaceous glands, dissolving in water and fats, being subjected to complex physico-chemical changes. Intact keratin layer acts as a pool, from which drugs penetrate deeper into the skin—into the dermis, where the vascular network transfers the drug molecules to the organs\(^3,11\).

Large blood vessels are in the hypodermis. In order to penetrate the systemic bloodstream, the drug substance has to overcome the multi-layered skin barrier. This can be achieved in several ways: transepithelial (i.e., through the cells of the stratum corneum of the epidermis), transfollicular (through the hair follicles or ducts of the exocrine glands) or intracellular. Most drugs penetrate into the skin by transepithelial way, which requires the passage of difficult lipid matrix\(^1-3\). Through the hair follicles, the ducts of the sebaceous and sweat glands (they constitute <1% of the skin surface) passes from 0.01% to 0.1% of the substances passing through the stratum corneum\(^16\).

The increased interest in transdermal pharmacotherapy is associated with the significant advantages of this form of drug delivery compared to injectable and enteral administration. Among the benefits of transdermal drug delivery are: (1) Exclusion of rapid metabolism when drugs get into the body, not counting the liver (the hepatic first-pass effect). (2) Minimizing or completely eliminating local and systemic side effects; in particular, the elimination of irritation of the gastrointestinal tract by the drug itself. (3) Reduction in the frequency of medication, reducing the required dose. (4) The possibility of rapid termination of the agent by removing it from the skin surface with undesirable reactions. (5) The possibility of point delivery of medicinal substance to specific areas of the human body (with joint diseases, when it is applied to biologically active points). (6) Freedom of action—you do not need to memorize the time and the amount of medicine taken. (7) Faster delivery of the active substance and therapeutic effect in relation to the diseased organ or organ system compared to the use of per os (by mouth) drug. (8) Continuous delivery and concentration of the active substance in the blood. (9) Improving the compliance of patients (an easy way to use the drug). (10) The anxiety component is excluded and there are no traumatic factors (for example, with intramuscular or intravenous injections, an easy way to use at home). (11) There are no violations by the patient of the curative regime. (12) Transdermal delivery for some drugs is the only way to enter the body. (13) Transdermal administration of medications is the most convenient way for patients with chronic diseases requiring constant medical treatment. (14) The minimum cumulative effect with prolonged use. (15) Efficiency (purposeful use of drug substances can reduce the required number in 100 times, and sometimes—in 1000 times) while maintaining the effect.
that makes the treatment cheaper and unique drugs more accessible.\textsuperscript{1,11,17–23}

However, transdermal drug delivery has a number of limitations: (1) Transdermal forms can cause an individual allergic skin reaction to the active substance or pharmacologically inactive components of the system. (2) It takes more time to start the transdermal drug operation than when injecting drugs. (3) Medicinal substances should have certain physico-chemical properties. The molecule should be neutral, since the negative and positive charges may interfere in its progress along the hydrophobic stratum corneum. The drug should have sufficient solubility in the hydrophobic stratum corneum and the hydrophilic dermis. The molecule should be relatively small—with not more than 500 D molecular mass\textsuperscript{1,2,7,24}. Specially developed technologies are required to deliver such drugs through the skin.

**TRANSDERMAL THERAPEUTIC SYSTEMS**

Currently, drugs are injected through the skin primarily through transdermal therapeutic systems (TTS). The TTS is a dosed soft dosage form for external use in the form of patches or films. It is characterized by a controlled release of the active substance. It is capable continuously feed a medicinal substance into the body and create a constant level of its concentration in the bloodstream, close to the minimum therapeutic level. They are mainly produced in the form of emplastrums\textsuperscript{1,5,7,11}. The TTS has a base and a medicinal substance.

As a rule, TTS consists of the following main components: (1) Polymer matrix/active substance reservoir. Polymers are the basis of the patch and they control the release of the active ingredients. Natural polymers (cellulose derivatives, chitosan, etc.) and synthetic polymers (polyacrylate, polypropylene, etc.) are used. (2) Active substances are medicines. (3) Enhancers—increase the permeability of the stratum corneum, interacting with the structural components of the epidermis (proteins, lipids). (4) Adhesive layer—provides close contact between the transdermal system and the skin surface. Polycrylates and silicone are widely used for this purpose. (5) Laminate (vinyl, polyethylene and polyester) gives the flexibility to TTS, it transmits the oxygen and it does not interfere with moisture evaporation. (6) Protective layer—immediately removed before applying TTS to the skin\textsuperscript{7,11,24}.

Transdermal therapeutic system is divided into two main groups: matrix and membrane\textsuperscript{2,11}. Membrane TTS consists of an impermeable substrate, a drug reservoir, and a membrane that regulates the release of the drug and an adherent (coherent) layer. The medicinal substance is in the reservoir in the form of a suspension in a liquid or gel. The reservoir is located between the impermeable substrate and the membrane of the porous polymeric foil, which determines the release rate of the drug substance.

The drug substance is placed in a matrix (TTS) consisting of a gel or a polymer film. The release of a drug substance from such a system is determined by its diffusion from the matrix material.

The various types of transdermal patches have been developed for many drugs. These include: (1) Single layer drug in adhesive (adhesive layer contains medicinal product). (2) Multi-layer drug in adhesive. (3) Vapor patch\textsuperscript{5,6,11,22,24,25}.

Unfortunately, the barrier properties of the skin make it impervious for many drugs and restrict the use of the transdermal delivery system\textsuperscript{11,22,26–28}. From this point of view, it is important to develop means that increase the skin’s permeability for drugs and preserve the skin’s immutability and its barrier function for such a system usage\textsuperscript{2,7,22}. It was proposed to change the properties of drugs, solvent or skin\textsuperscript{24,26,28}. For example, it has been shown that micro-emulsifiers increase skin permeability for drugs. Thus, a mixture consisting of water, oil and emulsifier forms a transparent optically isotropic and thermodynamically stable solution that improves the permeability of a number of drugs through the skin in the form of gels and emulsions\textsuperscript{22,23,29–31}.

Over the last years, a large number of new peptide and protein drugs have appeared. Their use is difficult due to: rapid removal from the blood, the large molecular weight, and these drugs are easily destroyed by proteolytic enzymes, tend to aggregate, undergo adsorption and denaturation\textsuperscript{9,23,24}. The transdermal matrix delivery system has many advantages over such methods as intramuscular or intravenous infusion exactly under such conditions. This method of drug delivery allows to prolong the time of its action, maintaining a constant therapeutic concentration of the drug\textsuperscript{24,25,32–34}.

The composition of TTS is made by various drug delivery enhancers that facilitate the penetration of active drugs through the skin barrier\textsuperscript{2,8,23,24,35}. The various measures are proposed in order to overcome the skin barrier for large, hydrophilic components, including not only chemical promoters (lipid solvents), but also through the use of various types of energy. Among them are: iontophoresis, electrophoresis, phonophoresis, focused ultrasound, thermal and laser ablation, radio frequency or various approaches to skin microorganization\textsuperscript{24,35,36}. The iontophoretic method of transdermal administration is the most preferred among these measures\textsuperscript{24,36,37}. The possibilities of chemical engineering that can make a significant contribution to the study of this complex problem\textsuperscript{4,9,15,23,24,35,39}.

The possibility of transdermal drug delivery using microneedles in combination with iontophoresis is considered\textsuperscript{35}. The ion pairs of complexes (ion-pair complexes) are widely used now in the transdermal drug delivery system\textsuperscript{35}.

One of the advantages of transdermal drug administration is the approach to optimal drug therapy, for which the time of drug injection plays an important role. The concept of chronobiology, chronopharmacology, homeostasis and chronotherapy can be fully realized by...
using the method of transdermal drug delivery into the body.\textsuperscript{10, 15, 22, 38–42}

A special heat-sensitive membrane coated with a drug is applied to stimulate the injection of the drug at the right time. Special membranes are used to create “patches” (emplastrums) with drugs placed on them in the form of gels. The creation of a drug reserve on the skin, from which the drug progressively flows through the skin into the blood, holding the therapeutic concentration for a long time is achieved by this method.\textsuperscript{1, 7, 11, 15, 39, 41, 42} Such patches are used to inject drugs for chronic diseases. These drugs include antidepressants, analgesics, hypoglycemic drugs, non-steroidal anti-inflammatory drugs, nootropics, acetylcholinesterase inhibitors, hormones, and antioxidants that do not stay in the skin by simple application by rubbing or applying.\textsuperscript{6, 11, 22, 35–41, 43, 44}

The technique of preparing membranes that slowly pass the drug through the skin (rate controlling membranes) is important for the transdermal drug delivery system. The composition of such membranes depends on the bioavailability of a particular preparation, which is determined by the physico-chemical properties of the drug itself.\textsuperscript{10, 15} In particular, the process of drug release through the membrane, its penetration through the skin, the moisture content of the membrane, the hygroscopicity of the membrane, the content of the drug in the membrane, the interaction of the drug with the membrane itself, and the density of the membrane are important. The area of the transdermal lining (12 cm in average)\textsuperscript{7, 44}.

The listed properties of transdermal drug delivery (particularly with the help of patch, needles) are studied using biochemical, histological, physico-chemical and other methods both in vivo and in vitro.\textsuperscript{2, 5, 35, 39, 40, 45}

As a matrix of transdermal membranes, various combinations of polyvinyl pyrrolidone, ethyl cellulose, ethylene vinyl acetate, Eudragit RL-100, Eudragit RS-100\textsuperscript{41, 46}. Transdermal therapeutic systems based on gelatin and polyacrylamide bases, as well as reservoir type systems using porous polymeric material\textsuperscript{2, 5, 7}.

The correctness of the composition’s choice of TTS in each individual case is controlled by clinical efficacy and pharmacokinetic studies.\textsuperscript{5, 9, 10, 36, 39, 40, 45} The gel containing various concentrations of the drug is administered carbopol, triethanolamine, water, ethanol, etc. These substances are applied to the membrane to form a transdermal patch.\textsuperscript{2, 6, 7, 47}

It has been established that the degree of penetration of certain drugs may depend more on the properties of the formulation and the solvent, rather than on the physico-chemical nature of the drug.\textsuperscript{48} Transdermal delivery systems based on liposomes were developed using pH-responsive phytosterol derivatives.\textsuperscript{49}

In recent years, convenient and easy-to-use delivery platforms in the form of microneedles have been developed. It significantly expands the range of drugs for transdermal transport.\textsuperscript{47, 48, 50–52} Solid and hollow versions of microneedle variant provide delivery of both small and large molecules, including hard-to-reach water-soluble substances.\textsuperscript{50}

These solid microstructured transdermal systems consist of an array of 316 microneedles that deliver abaloparatide. Recently, positive results of the clinical use of TTS for the treatment of osteoporosis were presented. These solid microstructured transdermal systems consist of an array of 316 microneedles that deliver abaloparatide (3M’s solid microstructured transdermal system (sMTS), which consists of an array of 316 microneedles). The use of the drug significantly increases the amount of bone mass in the spine and thigh of patients during 24 weeks of treatment.\textsuperscript{51}

A promising area is the development of anabolic therapy of osteoporosis with the transdermal route of administration teriparatide. This will avoid the burden of daily subcutaneous injections.\textsuperscript{52}

Microneedles coated with antigens are used for immunotherapy. In addition, microneedles coated with anti-cancer drugs can be used to spread the drug in the area of a malignant tumor. This can lead to regression of the tumor.\textsuperscript{53}

The TTS with an antiallergic drug morin is effective in treating contact dermatitis, which has been shown in animal studies.\textsuperscript{54} The TTS for local anesthesia can reduce the dosage of anesthetic (ropivacaine) and enhance the anesthetic effect.\textsuperscript{37} Lidocaine, injected by the transdermal, is effective in treating the syndromes of neuropathic pain, chronic pain, postoperative pain and refractory pain in oncology.\textsuperscript{58}

A combined transdermal system has been developed for the simultaneous delivery of two poorly soluble antihypertensive drugs (valsartan and nifedipine)\textsuperscript{59}.

Currently, preclinical trials of new antimicrobial nanoemulsion “oil-in-water” for external application on burn wounds are conducted. Nanoemulsion significantly reduces the growth of bacteria in the exudate burn wound and significantly reduces the number of inflammatory cytokines in the model of rodents and swines. The use of nanoemulsion will be a significant breakthrough in the treatment of thermal burns. This will reduce the need for skin transplantation, accelerate the restoration of damaged tissue, lead to a reduction in infectious complications and improve outcomes for many burn patients.\textsuperscript{51}

Now new vaccine delivery systems are being developed.\textsuperscript{60} Recently, the first clinical trials of a new trivalent inactivated influenza vaccine have been successfully conducted. The vaccine was administered transdermally with help of a patch with soluble microneedles. Participants were randomly assigned (1:1:1:1) to four groups and received a single dose of inactivated influenza vaccine (flurinirin: 18 μg of hemagglutinin per H1N1 vaccine strain, 17 μg of hemagglutinin per H3N2 vaccine strain, and 15 μg of hemagglutinin per B vaccine strain) and placebo by microneedle patch. A good immune response was established. Thus, the seroconversion percentages were significantly higher at day
28 after microneedle patch vaccination compared with placebo and were similar to intramuscular injection.61

Transdermal delivery of vaccines into the skin with the use of needles allows the introduction of a biologically active molecule of different physical size. The microneedle sites can be coated or encapsulated with a DNA vaccine, a subunit antigen, an inactivated or live virus vaccine.62

A promising method for treating multiple sclerosis is the use of transdermal myelin peptides patches, which modulates autoimmunity. In patients receiving myelin patches, decreased inflammatory activity of the brain on magnetic resonance tomography and a decrease in the frequency of relapses was observed. The significant changes in the morphology of Langerhans cells and shifts in the dendritic cell populations in the draining lymph nodes were observed.63

Currently, a new problem related to the application of the TTS is being discussed. How to dispose the means of transdermal drug delivery and how safe are they for the environment? There is a view that unused medicines, including controlled substances in patches, can safely be discarded, since they do not pose a danger to the environment.64

Active work is underway to develop microneedles for the delivery of drugs to the intratissue structures and joints for rheumatoid arthritis.65 The anti-inflammatory and analgesic effect of TTS in an experiment on rats with induced rheumatoid arthritis was demonstrated in preclinical studies in rats.66

The positive effector of the transdermal rotigotine patch is shown, which provided a significant improvement in nighttime hypokinesia symptoms in Parkinson’s disease.67

The prospect of future development of transdermal therapy for management of cognitive and behavioral dysfunctions in patients with Alzheimer’s disease, including long-term rivastigmine patch therapy was demonstrated in preclinical studies in rats.68

Nanoeumulsions have been developed to increase solubility, improve bioavailability and reduce the toxicity of slightly soluble antituberculous agents.69

The drugs for transdermal introduction of bacteriophages are developed. The high antimicrobial efficacy of bacteriophages T4 specific for E. coli, which was delivered using a microemulsion as the delivery vehicle was demonstrated in preclinical studies in rats.70

It should be noted that, despite a significant increase in the use of modern forms of TTS; however, the traditional methods of introducing drugs through the skin in the form of ointments, gels, suspensions, liniments continue to be used now.21,24,16,70

CONCLUSION

Thus, the transdermal method of delivering drugs for therapeutic purposes into the body remains relevant, and in some cases, it is the only acceptable variant (peptide, protein drugs). The advantages of this method of pharmacotherapy make it very promising for wide application in medicine. Transdermal drug delivery systems in the body using various technological methods are developed to ensure prolonged action of drugs. However, the development of such systems is not excluded the use of traditional transdermal administration to the body of a number of drugs by rubbing into the skin, applications, iontophoresis and ultrasonic.

FINANCIAL SUPPORT

The employer is the Ministry of Health of Russia.

REFERENCES


