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THERAPEUTICAL APPLICATION OF TRANSDERMAL SYSTEMS THAT PRESENTED ON US PHARMACEUTICAL MARKET

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Abstract

The development of new dosage forms with the active pharmaceutical ingredients that are immobilized on polymeric carriers - drug films that are used in various fields of medicine is gaining considerable popularity in the world. Transdermal therapeutic systems are designed to deliver the active pharmaceutical ingredient through the skin to achieve a systemic effect, an example of these transdermal therapeutic systems are buccal, dental, oral drug films. The main advantage of using fast dissolving oral forms is the possibility of their use by patients with dysphagia.

The study examines the scientific publications of the last decade, and the analysis of the range of drugs available on the US pharmaceutical market.

The range of medical films on the US market is formed as follows: 74% transdermal films, 11.1% - transdermal systems, 14% of the range - buccal and sublingual films, 0.9% - oral films. In the US pharmaceutical market, 33.63 % of the range of medical films has used to relieve the pain of various origins. The share of the transdermal system containing estradiol is 26.55 %, estradiol and its combinations in the form of films are used to treat the manifestations and symptoms of estrogen deficiency in postmenopausal or artificial menopausal women. The share of the transdermal systems for the treatment of neurodegenerative movement disorders is 15.49 %.

Transdermal drug delivery systems provide an attractive alternative to the oral route of delivery of biotherapeutic drugs. A focus on the further development of drugs in the transdermal system remains the finding of sufficiently potent drugs that can penetrate the skin or tissue with appropriate technology.

Keywords: *transdermal film, delivery system, buccal film, oral film.*

Introduction

The development of new dosage forms with the active pharmaceutical ingredients that are immobilized on polymeric carriers - drug films that are used in various fields of medicine is gaining considerable popularity in the world [1]. These dosage forms are an example of transdermal therapeutic systems that are designed to deliver the active pharmaceutical ingredient through the skin to achieve a systemic effect and differ from traditional topical therapy [2]. The principle of action of transdermal therapeutic systems is the transport of the active pharmaceutical ingredient through the skin through passive diffusion, because of which, by changing the concentration gradient, the active pharmaceutical ingredient diffuses from the matrix or diffusion medium and enters the human body [3, 4].

In addition, an example of these transdermal therapeutic systems are buccal, dental, oral drug films. Oral films are mono- or multilayer plates made of suitable materials, which are placed in the oral cavity, where they rapidly dissolve. After absorption through the mucous membrane of the oral cavity, the drugs enter directly into the systemic circulation, by passing the gastrointestinal tract [5, 6]. Buccal films belonging to mucoadhesive drugs, presented in the form of mono- or multilayer plates, intended for systemic absorption through the buccal mucosa during prolonged time [7]. Buccal administration involves placing a drug between your gums and cheek, where it dissolves and is absorbed into your blood [8]. Dental medicated films are also a type of transdermal therapeutic system and are used by the application to the mucous membrane of the oral cavity and periodontium for analgesia in epithelial tissue lesions [8, 9]. Sublingual or buccal drugs can be prescribed because of the following circumstances: the drug needs to get into your system quickly; you have trouble swallowing medication; the medication does not absorb very well in the stomach; the effects of the drug would be decreased by digestion [10].

The described therapeutic delivery systems of drugs have a number of advantages over traditional dosage forms and oral systems of controlled delivery of active pharmaceutical ingredients [11]. In particular, such systems provide faster action of active substances; avoidance of the effect of the first patency of the liver and gastric metabolism; ease of rapid identification of drugs in emergencies; control over the rate of penetration of the drug through the skin; the ability to constantly maintain the concentration of the active pharmaceutical ingredient in the blood; if necessary, reduce the dose of drugs; minimization or complete elimination of local and systemic side effects; obtaining a smaller effect of potentiation or weakening of the pharmacological action of the drug with prolonged use; convenience and ease of use [12, 13].

Transdermal therapeutic drug delivery systems also have advantages over injectable drugs; the administration of such drugs accumulates hazardous waste and, accordingly, creates a certain risk of transmission of the disease with a reusable needle [14].

Quick-dissolving oral dosage forms, by definition, when dissolved in the oral cavity, dissolve or disintegrate rapidly to form a solution or suspension without the need to add water. The oral cavity creates a unique environment for drug delivery. The mucous membrane of the oral cavity provides direct access to drugs into the systemic bloodstream, avoiding the first level of metabolism. Research in the direction of creating delivery systems for drugs in the oral cavity allowed developing of the technology of instant dispersible tablets, capsules, and films [15, 16].

The main advantage of using fast dissolving oral forms is the possibility of their use by patients with dysphagia. It is estimated that 35 % of the total population, which is 30-40 % of elderly patients, suffer from dysphagia. This disorder is associated with many diseases, including stroke, Parkinson's disease, AIDS, thyroidectomy, radiation therapy, neurological disorders, including cerebral palsy. [15, 16, 17].

Fast dissolving oral films are very thin films with an area of 5-20 cm2, which patients can place on the tongue or mucous membrane in the oral cavity. Saliva, which moistens the film, leads to its rapid hydration and adhesion to the application site. Fast dissolving oral films have been developed based on transdermal patch technology [6, 15, 17]. There are three different subtypes of Fast Dissolving Oral Films: Flash release; Mucoadhesive melt

release; Mucoadhesive Sustained release. A typical formulation contains the following ingredients: Drug; Film forming polymers; Plasticizers; Saliva stimulating agent; Sweetening agent; Flavouring agent; Surfactant; Colors; Filler. [18] The film composition usually contains a drug concentration of about 5-30 %. Drugs having small doses are the ideal candidates for incorporation in mouth dissolving films and should possess good stability and permeability through oral mucosa [19].

Advantages of oral films: available in different sizes and shapes, are thin; characterized by excellent mucoadhesion; dissolve quickly within minutes in the mouth; do not need water for swallowing; allow to mask taste; almost do not leave a residue in the mouth; are effective to ensure a rapid onset of action in sudden episodes of allergic attack or cough, bronchitis, asthma; characterized by increased bioavailability, especially in cases of insoluble and hydrophobic active pharmaceutical ingredients, due to rapid disintegration and dissolution; increase patient compliance [18, 19].

The main disadvantages of oral films are that they cannot include medicinal substances that are unstable at the pH of the oral cavity, irritate the mucous membrane or have a bitter taste, or cannot be introduced in large doses; films need special packaging to protect against water and shock [15-19].

Methods

In conducting the study, we used the method of primary information collection. Data from more than 96 sources were analyzed and summarized; in this research, 38 sources of modern foreign literature on the feasibility of using a transdermal drug delivery system were used. The study examines the scientific publications of the last decade, which are available on the Internet, the key words were "transdermal drug delivery system", "sublingual drugs", "buccal drugs" and "oral films". The study was conducted in October 2021.

The analysis of the range of drugs available on the US pharmaceutical market was performed on the basis of data from online directories [20]. The object of the study was information on registered drugs in the United States. Research methods used: generalization, systematization, comparative analysis. Commonly used methods of descriptive statistics were used for the study.

Results and Discussion

The US pharmaceutical market was chosen to study the range of medical films, as it is a key market in terms of drug costs, in particular for their development and implementation, as well as taking into account the localization of key pharmaceutical manufacturers in this country.

The range of medical films on the US market is formed as follows: 74% transdermal films, 11.1% - transdermal systems, 14% of the range - buccal and sublingual films, 0.9% - oral films.

The list of active ingredients that are part of the medical films is given in Table 1.

In the US pharmaceutical market, 33.63 % of the range of medical films has used to relieve the pain of various origins. These include transdermal films containing fentanyl, buprenorphine, their combinations with naloxone and ketoprofen.

Transdermal fentanyl films with different dosages for extended-release are available on the US pharmaceutical market. In 2019, Duragesic® for transdermal use and Onsolis® for buccal use had registered on the market.

Transdermal forms of fentanyl are used for the treatment of chronic pain. Transdermal fentanyl includes a lower incidence and impact of adverse effects, improved quality of life, and convenience of use. It is a useful analgesic for cancer patients who has swallow problems. Transdermal films form a depot in the upper layers of the skin before entering the microcirculation. Therapeutic blood levels are attained 12-16 hours after patch application and decrease slowly with a half-life of 16-22 hours following removal [21].

A significant part of the range of transdermal systems are films containing buprenorphine hydrochloride. Trademarks Butrans® (by Purdue Pharma Lp.) and Buprenorphine (by Amneal Pharmaceuticals LLC, Aveva Drug Delivery Systems Inc., Teva Pharmaceuticals Inc) provide transdermal delivery of medicine. They also presented buccal films Belbuca® (by Biodelivery Sciences International Inc.) and Buprenorphine (by Alvogen Inc.). The combination of buprenorphine and naloxone has presented on the US

pharmaceutical market in the form of films for buccal and sublingual use. The transdermal buprenorphine system induces dose-related pain relief, whatever the nature of the pain and the age of the patient. Buprenorphine also exerts an analgesic action on neuropathic pain [22].

The oral nonsteroidal anti-inflammatory drugs are effective in the treatment of a variety of acute and chronic pain conditions. Oral films of ketoprofen with the trade name Nexcede® (Novartis Consumer Health Inc.) have been marketed.

The share of the transdermal system containing estradiol is 26.55 % of the range of medical films on the US pharmaceutical market. In hormone replacement therapy, estradiol and its combinations in the form of films are used to treat the manifestations and symptoms of estrogen deficiency in postmenopausal or artificial menopausal women.

Medical films contain estradiol, which is presented under the trade names Climara® and Menostar® (by Bayer Healthcare Pharmaceuticals Inc.), Minivelle® (by Noven Pharmaceuticals Inc.), Vivelle® and Vivelle-dot® (by Novartis Pharmaceuticals Corp.), Esclim® (by Women First Healthcare Inc.), Estraderm® (by Novartis Pharmaceuticals Corp.), Fempatch® (by Parke Davis Pharmaceutical Research Div Warner Lambert Co), Alora® (by Allergan Sales LLC), Estradiol (by manufactures Mylan Technologies Inc., Amneal Pharmaceuticals LLC., Ortho Mcneil Pharmaceutical Inc.). Also registered transdermal films containing the combination of estradiol with norethindrone acetate (Combipatch®, (Noven Pharmaceuticals Inc.)). Combination of ethinyl estradiol with norelgestromin is presented under trademarks Ortho Evra® (Janssen Pharmaceuticals Inc)), Xulane® (Mylan Technologies Inc.) and Onsura® (Teva Pharmaceuticals Inc.). Combination of estradiol with levonorgestrel is known as Climara Pro® (by Bayer Healthcare Pharmaceuticals Inc.), and Twirla® (by Agile Therapeutics Inc).

Transdermal forms lead to higher bioavailability of estradiol compared with the oral use of medicines. The transdermal estradiol systems produce more physiologic levels of hormones than oral therapy and allows us to avoid the first-pass effect on hepatic protein synthesis. Transdermal forms produce favorable lipid profiles, prevent bone loss, relieve vasomotor symptoms, and improve urogenital atrophy [23, 24].

The share of the transdermal systems for treatment of neurodegenerative movement disorders is 15.49 % of the range of medical films on the US pharmaceutical market. Neurodegenerative movement disorders mainly include Parkinson's disease, atypical parkinsonism, Huntington disease, and hereditary ataxia. Transdermal systems of rivastigmine, rotigotine, selegiline, and apomorphine have been used to treat Parkinson's disease, dementia, and Alzheimer's disease.

Transdermal rivastigmine films have been marketed under the trademark Exelon® (by Novartis Pharmaceuticals Corp.) and Rivastigmine (by Alvogen Malta Operations LTD, Mylan Technologies Inc., Amneal Pharmaceuticals of New York LLC., Breckenridge Pharmaceutical Inc., Zydus Noveltech Inc.). Transdermal rivastigmine films provide significantly lower gastrointestinal side effects. That provides opportunities to continue treatment with higher doses of rivastgmine in advanced stages of Alzheimer's disease. Moreover, ease of use, easy-to-follow schedule, less administration time spent by the caregiver result in greater adherent to the treatment [25].

Rotigotine (trademark Neupro®), a non-ergolinic dopamine agonist, is administered once daily via a transdermal patch that delivers the drug over a 24-h period. The rotigotine is approved as monotherapy for the treatment of early Parkinson's disease and as a combination therapy with levodopa throughout the course of the disease [26].

Transdermal film of selegiline known as Emsam® manufactured by Somerset Pharmaceuticals Inc. Transdermal patches is effective in treating the major depressive disorder in adults and adolescents who are at least 12 years old [27].

Apomorphine is a dopaminergic agent and FDA-approved to treat off episodes in adults with Parkinson's disease. Kynmobi® is a brand-name sublingual film, which dissolves in about 3 minutes and releases the medication [28].

Amyotrophic lateral sclerosis is a progressive neurodegenerative disease caused by the death of motor neurons. Riluzole is used to treat amyotrophic lateral sclerosis. Riluzole is a benzothiazole derivative that blocks glutamatergic

neurotransmission in the central nervous system, which is thought to exert neuroprotective effects. Exservan® is a brand name of riluzole has been presented as oral films [29].

Asenapine is a novel antipsychotic that has demonstrated efficacy in controlling psychosis in schizophrenia and mania in bipolar illness. It must be administered as a sublingual formulation because it is nearly completely metabolized in the first pass through the liver [30]. Transdermal asenapine Secuado® has been approved for clinical use.

Nitroglycerin (glyceryl trinitrate) has been used for many years for treating acute anginal attacks. In recent years transdermal delivery of nitroglycerin has gained popularity for prophylaxis against angina. Transdermal nitroglycerin films are marketed under the trade name Nitro-Dur® (by Uspharma LTD) and others.

Clonidine transdermal films are known under the trademarks Catapres-TTS-1®, Catapres-TTS-2®, Catapres-TTS-3® (by Lavipharm SA) have registered in the US pharmaceutical market. Also presented transdermal clonidine system manufactured by Actavis Laboratories Ut Inc., Aveva Drug Delivery Systems Inc., Mayne Pharma LLC., Mylan Technologies Inc.

Transdermal clonidine, like oral clonidine, is effective in therapy for most forms of hypertension. More recently, transdermal clonidine has found alternative uses in the areas of smoking cessation, posttraumatic stress disorder, menopausal hot flashes, and alcohol and opiate withdrawal syndromes [31].

The range of transdermal systems based on nicotine, known as Habitrol® (by Dr. Reddys Laboratories SA.), Nicoderm CQ® (by Sanofi Aventis Us LLC), Nicotrol® (by Mcneil Consumer Healthcare), Prostep® (by Aveva Drug Delivery Systems Inc.), is quite wide.

Transdermal nicotine is effective for patients who are motivated to quit smoking and receive psychological behavior support. Habitrol®, Nicoderm®, Nicotrol® and Prostep® differ in some characteristics (i.e., delivery systems, total nicotine content and amount absorbed, rate of delivery, recommended duration of application) [32].

On the US pharmaceutical market, presented medical films that contain scopolamine or granisetron to prevent vomiting during cytotoxic chemotherapy.

Scopolamine became the first drug commercially available as a transdermal therapeutic system used for extended drug delivery during 72 h. Clinical trials with transdermal scopolamine have consistently demonstrated its safety and efficacy in postoperative nausea and vomiting [33]. Transdermal scopolamine film produces as brand name Transderm Scop® by Baxter Healthcare Corp. and as generics drugs Scopolamine by Mylan Technologies Inc., Padagis Us LLC., Riconpharma LLC.

Transdermal granisetron (trademark Sancuso®) is effective for the prevention of nausea and vomiting in patients with cancer who are receiving moderately or highly emetogenic chemotherapy for 3-5 days. The transdermal granisetron system delivers continuous granisetron (3.1 mg/day) into the systemic circulation (via passive diffusion) for up to 7 days [34, 35].

The methylphenidate transdermal system has been indicated for use in the treatment of attention-deficit hyperactivity disorder in adolescents aged 13-17 years [36]. The transdermal form of methylphenidate is known as a trading name Daytrana® (by Noven Pharmaceuticals Inc.).

Transdermal films of testosterone have been marketed with the trademark Androderm® by Allergan Sales LLC. A nightly application of the testosterone transdermal system in men with hypogonadism results in a 24-hour serum testosterone concentration profile which mimics the circadian pattern observed in healthy young men. The system also normalizes dihydrotestosterone/testosterone and estradiol/testosterone ratios and reduces luteinizing hormone levels towards the normal range [37].

Overactive bladder is a common and disabling problem. The mainstay of pharmacological treatment is using oral anticholinergic drugs. Transdermal administration of oxybutynin has been shown to be as effective as oral treatment while minimizing the anticholinergic side effects [38]. Transdermal film of oxybutynin has been known by trademarks Oxytrol®, Oxytrol for Women® (Allergan Sales LLC).

Conclusions

Transdermal drug delivery systems provide an attractive alternative to the oral route of delivery of biotherapeutic drugs. In addition, transdermal films are effective in administering drugs that have a high hepatic clearance or degradation in the gastrointestinal tract, as well as for patients who have difficulty swallowing.

Therefore, transdermal system have therapeutical applications for pain relief, correction of estrogen and testosterone deficiency, treatment of neurodegenerative movement disorders, hypertension, prevention of angina pectoris, smoking cessation.

A focus in the further development of drugs in transdermal system remains the finding of sufficiently potent drugs that can penetrate the skin or tissue with an appropriate technology.

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Table 1. List of international non-proprietary names of medicinal substances that are part of the films

Name of Active Ingredient	The share in the range of transdermal forms containing the specified active substance,%
Estradiol	21.1
Buprenorphine hydrochloride	15.0
Fentanil	12.4
Rivastigmine	8.0
Clonidine	6.6
Nitroglycerin	6.6
Combination of buprenorphine hydrochloride and naloxone hydrochloride	5.8
Nicotine	5.3
Rotigotine	2.7
Combination of ethinyl estradiol and norelgestromin	2.2
Apomorphine hydrochloride	1.8
Combination of estradiol and norethindrone acetate	1.8
Scopolamine	1.8
Methylphenidate	1.8
Asenapine	1.3
Selegiline	1.3
Combination of estradiol and levonorgestrel	1.3
Testosterone	0.9
Oxybutynin	0.9
Granisetron	0.4
Riluzole	0.4
Ketoprofen	0.4
Total	**100 %**

Figure 1. Distribution of drug films that are available on the US market for their intended purpose