IJPSR (2015), Vol. 6, Issue 8 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 December, 2014; received in revised form, 12 February, 2015; accepted, 26 April, 2015; published 01 August, 2015

CONSUMER PROPERTIES OF TRANSDERMAL PATCHES AND THEIR USE IN MODERN PHARMACOTHERAPY

T. V. Diadiun [*1], I.I. Baranova [1], S.V. Stepanenko [2] and M.V. Nikitina [3]

Commodity Science Department [1], Industrial Pharmacy Department [2], Cosmetology and Aromology Department [3], National University of Pharmacy, Kharkov, Ukraine

Keywords:

Transdermal Therapeutic Systems, Patches, Classification, Consumer Properties

Correspondence to Author:
T. V. Diadiun

Commodity Science Department National University of Pharmacy, 4, Blukher str. Kharkov, Ukraine

E-mail: trunovacommodity@gmail.com

ABSTRACT: In today's hectic lifestyle, such dosage form as plaster, attracts more attention of scientists and gives new opportunities to use it in medicine. The purpose of our study was to investigate consumer properties of transdermal patches, hold the commodity analysis of the dosage form and determine the prospectiveness of their use in modern pharmacotherapy. Market review has been conducted. Analyzed the producing countries of transdermal patches reported on the pharmaceutical market of Ukraine. An analysis of the active ingredients used in the TTS has been carried out. Modern classifications of transdermal therapeutic systems have been given. The approaches to creation of TTS have been investigated. The most important consumer properties of TTS have been specified.

INTRODUCTION: Treatment is inextricably linked with the question of the rational form choice in which the drug substance or complex of substances have to give pharmacological effect. Along with the expansion of the range of drugs and improving treatment methods has extended the range of dosage forms and improved their technology.

In today's hectic lifestyle, such dosage form as plaster, attracts more attention of scientists and gives us new opportunities to use it in medicine. The molecules of many medicinal substances can diffuse from the drug to the skin surface, penetrate the stratum corneum and reach the epidermis and dermis, followed by their transfer through vascular net to the organs and tissues.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(8).3314-20

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(8).3314-20

Through transdermal delivery is supported a stable concentration of a medicine in the peripheral circulation that compared with other dosage forms increases the safety profile of patches. The purpose of our study was to investigate consumer properties of transdermal patches, hold the commodity analysis of the dosage form and determine the prospectiveness of their use in modern pharmacotherapy.

Experimental section:

Plaster - dosage form as a plastic mass that has the ability to soften at body temperature and stick to the skin, or the same mass on a flat carrier, designed for topical use. This is one of the oldest dosage forms [1]. Patches at room temperature are solid masses. At body temperature, they soften, and at a temperature of 65-100 ° C - melt. Under these conditions, they can be fused with different medications and adjuvants and mix with powders. In addition, patches may be produced in the form of liquids in glass bottles, aluminium tubes, aerosol containers.

Patches depending on medical assignment are divided into:

1. Epidermal - in most cases do not contain medicinal substances; used to protect the skin from harmful effects for closing defects, convergence of wound edges and fixation of bandages on the surface of the skin.
2. Endermal - obligatorily contain drugs with different therapeutic effects (eg keratolytic, depilating et al.) used in diseases of the skin at the site of the overlay.
3. Diadermal - Contain drugs that penetrate the skin and act on deep tissues or produce a general effect on the body.

Patches are produced in the form of plastic masses on the substrate (canvas, chiffon, calico, paper, etc.); Solid adhesive mass (cylinders, rods, tiles, sticks); liquid solutions (skin glue).

The structure of the adhesive mass includes drugs and base. As drugs use antibiotics, sulphur, salicylic acid, extracts, tinctures, and others.

Adhesive base may include natural (rosin) and synthetic resins, wax, paraffin, ceresin, petrolatum, lanolin, lead salts of higher fatty acids (lead soap), fats, rubber, nitrocellulose, copolymers of vinyl pyrrolidone with vinyl acetate, acrylates and polymethacrylates, volatile solvents (ether, benzene, ethanol). It contains plasticizers (linetol, vegetable oil, dibuthyl phthalate, cetyl alcohol, etc.), antioxidants, fillers, etc. [2, 3].

Depending on the composition patches are classified as lead (lead-resin and lead-wax); resin-wax; rubber; liquid (skin glue). Manufacturing technology of patches depends on which group they belong to. Transdermal route of administration of drugs allows minimizing variability in the therapeutic effect, reducing the effect of presystem hepatic metabolism, applying a substance with a narrow therapeutic index and a short half-life period and eliminate the possibility of an overdose in the initial period of treatment and the associated frequency of manifestation of side effects .TTS - (transdermal therapeutic systems) allows to quickly create the required therapeutic concentration of drugs in the blood, and in the case of side-effects - to stop their incoming. Increase or decrease of the dosage of drugs in this is achieved by the imposition or removal of additional strips of TTS. No other type of existing therapeutic medical systems do not provide such a simple dose adjustment drug. When using TTS full dose of a substance that is outside the body, is only in contact with it, so this dosage form can be considered as one of the easiest and safest.

The process of absorption of substances through the skin depends on the intensity of blood flow and the chemical composition of the surface of the skin. When using TTS should take into account the physicochemical properties of drugs, physiological state of the skin (inflammation, extent of damage to the stratum corneum, permeability) and other factors. Carotene, which is formed in the cells of the epidermis determines its resistance to various mechanical, physical and chemical effects. It is also the main factor of "impermeability" of the skin to most substances that exist in nature. Lipids released by sebaceous glands, mixed with lipids of keratinocytes form on the skin surface lipid film, which provides bactericidity and impermeability of skin. A limitation to the use of TTS is that drugs have to show in low concentrations therapeutic activity and be easily absorbed through the skin, and the rate and extent of penetration depends on its functional state.

The bases of the existing TTS classifications are technological and pharmacokinetic principles.

Basic principle of the TTS creation is to control the speed of incoming of medicinal substances through the skin, regardless of individual differences in its permeability. To ensure constant release of drug substance from the TTS they have a reservoir and semi-permeable membrane that regulates the speed of materials inflow to the inter-phase "dosage form - the skin."Constancy of release is regulated by membrane properties (thickness, porosity, swelling, etc.). TTS placed on the skin, forms a double layer - the actual membrane and skin, which serves as a membrane. The intensity of the drug substance penetration through the skin barrier is largely determined by the physical and chemical properties of the penetrant: solubility, distribution coefficient, pH and so on. The motive force for diffusion is the concentration of drug in solution. The process of

absorption through the skin also depends on the solubility of the drug substance in water and fats. Fat-soluble drugs readily penetrate the skin, kept by adipose tissue, only a small amount of them gets into the bloodstream. Adipose tissue of skin is a barrier to diffusion of water-soluble medicinal substances into the systemic circulation. Thus, the partition coefficient of drugs in the system of o/w is paramount when designing the composition of the TTS.

The rate of diffusion depends on the degree of ionization of drugs. Not-ionized molecule of a drug substance diffuses through the skin faster than ionized one. Molecular size of drug substance also affects the ability to penetrate through biological and polymeric membranes. The nature of excipients used in TTS technology has a decisive influence on the rate and completeness of release of drugs. To accelerate skin absorption and increase the solubility of poorly soluble substances use DMSO, ethylene glycol monomethyl ether, glycerylmonooleate, methylpyrrolidone, polyvinyl pyrrolidone, formamide, etc. Activators of absorption should promote the release of drugs from the system, stimulate trans - cutaneous absorption of drugs. They should be released from the system and be compatible with its components, be chemically stable during storage, non-toxic and pharmacologically indifferent; should not irritate the skin and cause sensitizing effect.

Today there is industrial production of TTS with scopolamine - Transderm Scop (USA), which provides a release rate of scopolamine 0.5 mg for 3 days to prevent and treat motion sickness. When used TTS with scopolamine motion sickness in 75% of patients did not arise. At this side effects were manifested as a slight decrease in salivation. However, oral administration of scopolamine by 300-600 mg 4 times a day is accompanied by tachycardia, a sharp decrease in salivation, drowsiness.TTS Transderm-Nitro and Nitro-Dur - are multilayer laminated systems of membranes of 0.2 mm thickness (**Fig.1**).

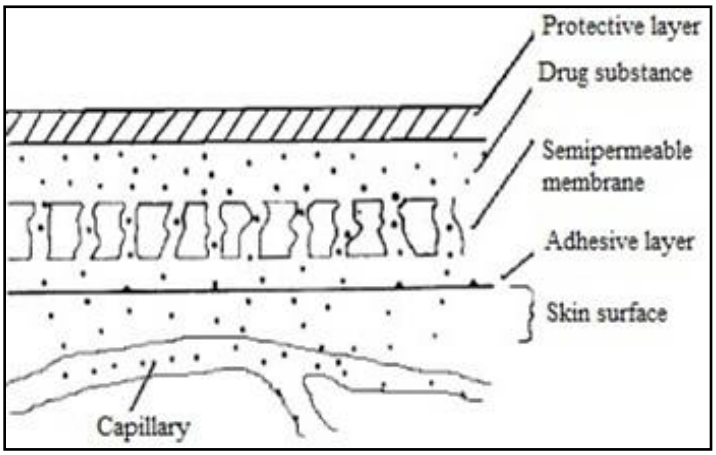

FIG.1: SCHEME OF TRANSDERMAL THERAPEUTIC SYSTEM

The outer layer of the system consists of aluminized polyester that prevents moisture getting in the TTS and evaporation of nitroglycerin. The reservoir contains nitroglycerin and lactose in a viscous silicone fluid. The membrane is made of ethylene vinyl acetate, and is permeable to nitroglycerin. Adhesive layer is made of silicone rubber. Industry produces TTS of two sizes - 10 and 20 cm 2.Amount of nitroglycerin available for dermal absorption is determined by the size of the TTS. The therapeutic dose of nitroglycerin is considered the release equal to 0.5 mg / cm 2 for 24 h. Has been designed TTS Catapres-TTS, providing a gradual release of clonidine during the week and capable of replacing conventional clonidine 0.5 mg tablets twice daily administration or a single dose of extended release tablets containing 0.25 mg of the API. The range of APIs that are introduced into the TTS, increases every year .The company "Alza" (USA) developed TTS for use in periodontal disease.

The system contains tetracycline. The company "Ciba-Geigy" has developed TTS with beta-blockers (oxprenolol, metoprolol), the duration of

which action exceeds 24 hours. Have been created TTS containing derivatives of benzodiazepine (diazepam, nitrozepam, medazepam, nimetazepam, lorazepam and others). TTS provide a constant release rate and exclude the possibility of adverse effects in their long-term use. A TTS Duragesic (Belgium) with strong analgesic has been developed. The TTS contains 0, 1-2% of fentanyl in 40% aqueous ethanol, solidified with hydroxypropyl cellulose. The membrane that regulates the diffusion flow of API is made of polyethylene and vinyl acetate. Company "Molekulon Biotech" (USA) produces TTS based on poroplastic that is a molecular sponge. The use of this membrane has allowed including to the TTS composition APIs for the treatment of angina and also anticontagious, antiallergic and analgesic agents. Thus, targeted delivery of drugs in the patient's body in the form of TTS provides optimal display of their pharmacological action and allows for individual therapy.

In the application of transdermal therapeutic systems should take into account not only the physical and chemical properties of a medicine, but the physiological condition of the skin (inflammation, extent of damage to the stratum corneum, permeability, age and ethnic differences, and so on.) [4, 5, 6].

The process of skin absorption of drugs depends on the intensity of the blood supply and the chemical composition of the surface of the skin. Blood supply of the skin comes from deep parts of the dermis. In the skin, the blood of 60% is venous. Healthy skin is a good barrier against adverse environmental factors. Keratin that forms in the cells of the epidermis, gives it resistance to a variety of mechanical, physical and chemical effects. Lipids pushed by sebaceous glands, mixed with lipids of keratinocytes form on the skin surface fatty lubricant that provides its permeability and bactericidal activity. In terms of physical and chemical laws of diffusion, the skin is considered as a simple membrane [7, 8, 9]. Release rate of medicines depends on the surface of skin area on which the medicine is located and the composition of the ointment bases and method of application of ointment.

The process of skin absorption depends on the solubility of a medicine in water and fats. Fat-soluble medicines easily penetrate the skin, kept by adipose tissue, and only a small part enters the bloodstream. Adipose tissue is a barrier to water-soluble substances. Therefore, topical is the use in such systems emulsion environments of type w/o or o/w.

Trends in research on the development of therapeutic systems:

- search for new polymeric materials;
- expanding the range of solvents;
- expanding the range of APIs applied in TTS.

Medicinal substances introduced into the body via the TTS should:

- have sufficient permeability through the skin to reach to blood flow in the required quantities;
- be highly effective, i.e. in small quantities to cause a therapeutic effect;
- have sufficient tolerance to skin;
- be suitable for prophylaxis, long-term use or replacement therapy.

At present, the international market has the following

TTS categories:

1. Systems based on semipermeable membranes (Transderm-nitro-TTS with nitroglycerin).
2. Polydisperse systems based on adhesives saturated with medicinal substances (Frandol - System with isosorbid-dinitrate).
3. Disperse systems based on polymer non-cohesive matrices that provide a given rate of diffusion (Nitro-dur system with nitroglycerin).
4. Polydisperse systems (microreservoir - system with nitroglycerin Nitrodisc) [4, 5].

If we consider the existing TTS in terms of the presence or absence of dosing membrane, which provides the most accurate system for creating constant concentration of drug substances, they can be divided into the following types:

- Reservoir or membrane (one reservoir, release of drug substances through the membrane);
- Matrix with uniform distribution of drug and polymer;
- Composed of numerous cells, the combination of the first and second types.

Membrane systems consist of a reservoir containing the drug substance and permeable polymer membrane that has a constant permeability by relation to the drug. The membrane can be both microporous, and monolithic. Outside on the membrane surface there is a layer of polymer adhesive that provides contact with skin. The release of drug substance is determined by its diffusion through the membrane.

Matrix systems, in contrast to the membrane ones, are more simple in a structural sense. In such systems, medicinal substance is dissolved or suspended in a matrix consisting of a gel or polymer film, the release is governed by diffusion of the active substance from matrix material [4, 5].

Conducted in recent years, biopharmaceutical studies have shown that adjuvants included in the dosage form, not only determine its properties, but also to a large extent influence the processes of absorption of drug substances and their therapeutic efficacy.

Excipients used in the creation of directed drug delivery systems are:

- various cellulose ethers that allow creating multi-layer compositions with different ability of polymer layers to degradation;
- propylcellulose and ethylcellulose blends in different ratios for microcapsules;
- poly-L-lactides with different molecular weight to get oral mikropelettes;
- copolymers of lactic and glycolic acids to obtain biodegradable porous microspheres for parenteral administration;
- water-soluble polymeric carriers based on N-(2-hydroxypropyl) - methacrylamide for selective delivery of drugs, etc. [4, 5].

Quality of TTS is controlled by the following parameters:

- Appearance;
- The area of the system;
- The rate of drug substance release from the system;
- Value of adhesion;
- The content of drug in the system;
- The thickness of the layer or reservoir with drugs, thickness of membrane, the residual moisture and so on. [1]

Test Uniformity of dosed units. Transdermal patches should withstand the uniformity of dosed units test (9.2.40) or, in justified and authorized cases the homogeneity of the content of active ingredient per unit of dosed medicine test as specified below.

This test is not applied to medicinal products containing herbal remedies and raw materials. Uniformity of content (2.9.6). Transdermal patches are tested to withstand the content uniformity of active ingredient per unit of dosed drug (test C), unless other is specified in a monograph. Dissolution to confirm appropriate release of the active ingredient (s) may be used suitable tests, for example, one of the tests described in the article "Test" Dissolution "for the transdermal patches" (2.9.4). As suitable may be applied test methods using a set of disks, cell or cylinder rotating, depending on the composition, size and shape of the patch. Can be used membrane. It can be made of different materials such as inert porous cellulose or silicones, and should have no effect on the kinetics of release of active substances from the patch. Moreover, membrane must be free from substances that can change its properties (such as oil).The membrane must be properly processed before the test, for example, it should be kept in used test medium within 24hrs. Membrane covers the release surface of patch avoiding the formation of air bubbles. Test conditions and requirements should be determined by the competent authority [1].

Storage

At room temperature, unless other indications [1].

Marking

The label, if necessary, indicates:

- The total amount of active ingredient (s) in patch;
- Dose released per unit of time.
- The release surface area of the patch.[1]

We have analyzed the producing countries of transdermal patches reported on the pharmaceutical market of Ukraine. Results of the analysis are shown in (**Fig.2**).

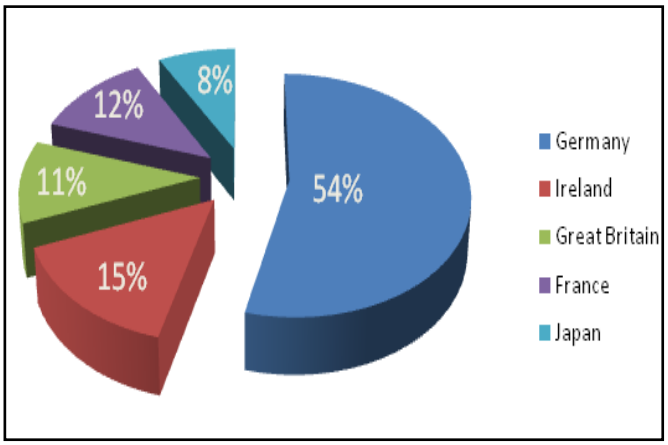

FIG. 2: ANALYSIS OF THE MANUFACTURERS OF TRANSDERMAL PATCHES

As we see the market of transdermal patches is completely represented by imported products, with most of German production. The absence of domestic production transdermal patches shows the need for the study and implementation of the dosage form by pharmaceutical companies in Ukraine. Also, an analysis of the active ingredients used in the TTS has been carried out. Results of the study are presented in (**Fig.3**).

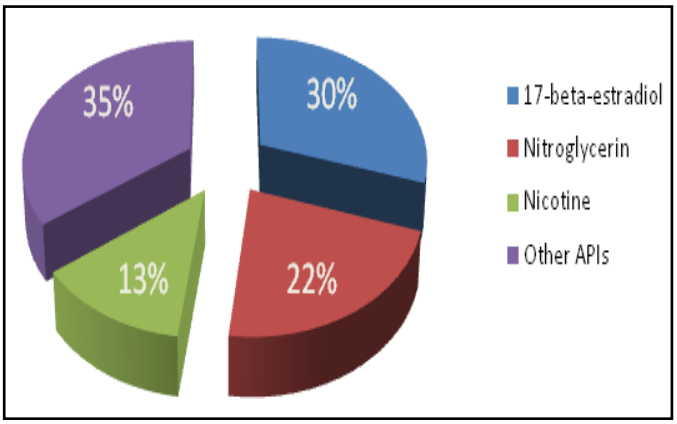

FIG.3: ANALYSIS OF ACTIVE INGREDIENTS USED IN TRANSDERMAL PATCHES

From this chart we can see that the main bulk of the TTS market is represented by three types of drug substances that also shows us the need for study of the dosage form, the search for new materials that can be used in TTS.

will grow. The increase in production is associated with the improvement of technology of transdermal administration of drugs and increase of their

The advantages of transdermal therapy

- The active substance is released so quickly and within such period of time as it takes to achieve the desired therapeutic effect;
- Reducing the effect of presystem metabolism in the liver;
- Ability to use materials with a narrow therapeutic index;
- Exclusion of the possibility of an overdose in the initial period of therapy;
- Provision of uniform drug concentration in plasma during the day;
- Easy and affordable way of application.

Some limitations of the method:

- The risk of local skin reaction - irritation, allergic urticaria, dermatitis due to idiosyncrasia;
- The drug takes effect over a longer period of time than when it is entered it through the injection;
- The loss of active ingredient during its transmission through the skin;
- The number of substances which may be administered using a transdermal patch is limited [7].

Today are marketed chondroitin patches against inflammation in the joints, and is being developed a range of transdermal patches intended for the treatment of various diseases. They are interferon patches for the treatment of viral infections, and patches of diclofenac to fight rheumatic pains, and xanomeline patches for the treatment of Alzheimer's disease and other transdermal systems used in neurology, psychiatry, dermatology, urology, andrology, gynecology, endocrinology and other areas of medicine [7].

CONCLUSIONS: Thus, transdermal therapeutic drug delivery systems are one of the most promising areas of pharmacy of the XXI century. The TTS range is constantly increasing - are issued TTS for the treatment of cardiovascular, hormonal diseases, for the treatment of nicotine addiction. It is estimated that global sales volumes of transdermal therapeutic drug delivery systems

functions diversity. The studies of consumer properties of transdermal patches had shown their superiority over other dosage forms due to their

convenience, efficacy, safety, ease and simplicity of use.

REFERENCES:

1. State Pharmacopoeia of Ukraine / State Enterprise "Scientific and Expert Pharmacopoeial Centre". - 1st ed. - H.: RIREH, 2001. - 531 p.
2. Industrial technology of drugs: Textbook. Chueshov V.I, Chernov N.E, Khokhlova L.N and others, Ed. prof. Chueshov V.I. - H.: Osnova; Publishing office of UkrPA, 1999. - 704 p.
3. Technology and standardization of drugs: Digest of scientific works/ SSCD; Hoskommedbioprom; Ed.V.P Georgievsky, F.A Konev. - H.: "Rireg", 1996. - 779 p.
4. Pharmaceutical and medical-biological aspects of drugs Ed.I.M. Pertsev, I.A. Zupanets. - Kharkov: Publishing office of the NPhAU, 1999. 2 (1): - 464 448.
5. Technology of dosage forms: Tutorial Bobylev R.V., Gryadunova G.P, Ivanova L.A and others, Ed. Ivanova L.A. - Moscow: Medicine, 1991.
6. Vasiliev A.E, Krasnyuk I.I, Ravykumar S.N, Tochmachy W. H. Transdermal therapeutic systems of drug delivery Chem.-pharm. Mag. - 2001. - 35, No 11. - P. 29-42.
7. Transdermal therapeutic systems Quality Clinical Practice. - 2001. - No 1 [Electronic resource]. - Mode of access: http://medi.ru/doc/991011.htm
8. Hsieh DST Subcutaneous Controlled Delivery of Estradiol by Compudose Implants: In Vitro and In Vivo Evaluations. Drug Develop & Ind. Pharm. 13: 1987.
9. Keith AD Polymer Matrix Considerations for Transdermal Devices / / Drug Develop & Ind. Pharm. - 1983. - Vol. 9;
10. Ogiso T., Ito Y., Iwaki M., Yamamoto Y. Membrane-controlled transdermal therapeutic system containing clonazepam and anticonvulsant activity after its application. Chem. Pharm. Bull. (Tokyo). -1989. - 37, No2. -P. 446-449.
11. Potts RO, Cleary GW Transdermal drug delivery: useful paradigms. J. Drug Target. - 1995. 4. P 247-257.
12. Ranade VV Drug delivery systems.J.Clin.Pharmacol.-31(5):1991401-418.
13. Chien YW. Transdermal therapeutic system. In: Robinson JR, Lee VHL, editors. Controlled Drug Delivery Fundamentals and Applications. 2nd ed. New York, NY: Marcel Dekker; In 1987. Pp.524-552.
14. Aqil M., Sultana Y, Ali A, Dubey K, Najmi KA, Pillai KK. Transdermal drug delivery system of a beta blocker: design, in vitro, and in vivo characterization. Drug Deliv. 2004; 11:27-31.
15. Keith A.D. Polymer matrix consideration for transdermal devices. Drug Dev Ind Pharm. 1983, 9:605-621.

How to cite this article:
Diadiun TV, Baranova II, Stepanenko SV and Nikitina MV: Consumer Properties of Transdermal Patches and Their Use in Modern Pharmacotherapy. Int J Pharm Sci Res 2015; 6(8): 3314-20 doi: 10.13040/IJPSR.0975-8232.6(8).3314-20.