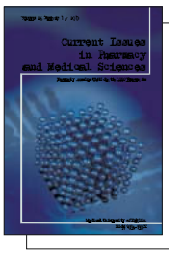

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# A review of TTS – development, types and preparations

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**ABSTRACT**

Transdermal Therapeutic Systems (TTS) are elastic multi-layer patches applied to the skin in order to deliver active substances into the bloodstream. One advantage of a transdermal drug delivery route over other types of medication delivery is that the patch provides a noninvasive therapy, longer duration of drug activity, and improves most of bioavailability. TTS consist of a backing layer, a drug, an adhesive, and a release liner. TTS can be divided into five basic types of systems: reservoir, matrix, microreservoir, single-layer drug in adhesive, and multi-layer drug in adhesive. In order to improve the penetration of drugs through the skin, passive and active methods are used. The researchers are constantly developing new methods of improving the delivery of drugs applied by transdermal route.

**Keywords:** transdermal therapeutic system, transdermal drug delivery, permeation enhancers, active techniques, technology solutions

## INTRODUCTION

Transdermal Therapeutic Systems (TTS) are elastic multi-layer patches applied to the skin in order to deliver active substances into the bloodstream after penetration of skin barrier [25,39]. The active substance is released at a predetermined rate and at a specified time. During this time TTS provide a constant concentration of the drug [30].

TTS have several important advantages over more traditional approaches [3,6,22,42]. They are simple, easy to use, and noninvasive. This sort of drug delivery improves a patient's compliance in chronic treatments. The therapy is safe. Just by removing the patch it is possible to terminate potential toxicities of the drug (such as drug allergies). TTS eliminate potential gastrointestinal side effects of oral dosage forms. The drug is absorbed directly through the skin and delivered to the blood or lymphatic system. TTS ensure constant plasma drug concentrations and eliminate pulsed entry into systemic circulation. Bioavailability is improved by avoiding first-pass hepatic metabolism and enzymatic or pH-associated deactivation. Transdermal delivery not only provides a controlled, constant administration of the drug, but also allows a continuous input of drugs with short biological half-lives and low therapeutic index.

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Local irritation at the site of application, erythema, itching, and local edema are the main disadvantages of transdermal drug delivery systems. Possible hypersensitivity reactions include irritant contact, allergic contact, and allergic contact urticaria [26]. The patient should follow recommendations about the site of drug application. Alternating application sites is the most important preventive measure against hypersensitivity reactions. Developing a rotational system for the area of patch application seems to be the best solution to the problem. It is important to maintain the skin barrier function and try to avoid skin irritation. Baths and showers should be limited to 5-10 minutes only and emollients should be used to moisten the skin. Patches should be removed gently. An oil-based product like petroleum jelly can be used to remove any residual adhesive [26].

## CURRENTLY USED DRUGS

Transdermal patch technology has advanced since the first scopolamine patch was introduced to the market in 1979. The success of nicotine patches revolutionized the use of transdermal drug delivery. Nowadays the advanced technology of patches production guarantees that nearly a billion patches are manufactured every year [40].

Table 1. shows the therapeutic substances present in the commercial preparations, for example nitroglycerin, clonidine, oestradiol, fentanyl, and nicotine.

In 1992, the nicotine transdermal delivery system was introduced to help treat tobacco dependence. All the patches release a controlled amount of nicotine through the skin. The constant plasma nicotine concentration reduces the nicotine cravings and can help abstain from smoking. Nicotine is a suitable candidate for transdermal therapy because it is highly soluble in lipids, and permeates the skin easily [12,50].

Transdermal contraception has provided an important new therapeutic option for many women. A currently common marketed contraceptive patch consists of a matrix system that releases the progestin norelgestromin and ethinylestradiol. A lower dose may reduce the incidence of side effects, but current data are too limited to support this claim. Recent epidemiological data indicate a slight increase in the risk of venous thromboembolism in patch users compared with oral contraceptive pills users [21,41]. The drugs administered orally must be taken at least once a day. The transdermal contraceptive patch offers an alternative for women who seek a hormonal contraceptive that may be easier to use and perhaps more suitable for contemporary, active lifestyles [10,49].

The use of analgesics as a 'pain relief patch' is also gaining popularity. When applied to the skin, these patches can deliver an analgesic drug at a predetermined rate across the dermis to achieve either a local or systemic effect. Transdermal analgesics are now used in many areas of pain management and by many different patient groups. The application of a local anaesthetic patch is particularly useful in pediatric practice to prevent the pain of venesection or vaccination. Localized transdermal delivery of drugs may be helpful in the management of chronic neuropathic pain, for example topical capsaicin and lidocaine patches. Transdermal analgesics can be used for the treatment of the chronic nociceptive pain. Fentanyl and buprenorphine (opioid analgesic) have been available for many years in a patch form. They are important especially in the treatment of cancer pain. There is a non-steroidal anti-inflammatory drug (NSAID) patch containing 1% diclofenacepolamine. It can be used for local treatment of pain in epicondylitis and ankle sprain. Topical NSAIDs are formulated in a way so that they penetrate the subcutaneous tissues and accumulate under the site of application. A local treatment prevents severe risk of gastrointestinal ulceration, bleeding, and perforation associated with the use of oral forms of NSAIDs [4].

Transdermal form of the drug is particularly important in the pediatric practice and in the treatment of older people for example in the treatment of ADHD, menopause, Parkinson's disease and Alzheimer's disease.

## COMPONENTS AND TYPES OF TTS

The basic components of TTS are [13,36]:

- backing layer – protects against outer factors (polyvinyl and polyethylene films),
- drug/drugs,
- adhesive – allows stick patch to the skin (silicons, gums, acrylates),
- release liner – protects adhesive layer, is removed before its use (polymer impregnated paper coated with a silicone).

Transdermal Therapeutic Systems may be divided into [13,25,36]:

**Reservoir system**

This type of the drug is contained in a reservoir between the backing layer and the polymeric membrane. This membrane, connected to the reservoir, is a controlling release element. The drug is suspended or dissolved in a solvent or in a polymer. Materials used for production of the membrane are copolymers of vinyl acetate and ethylene or methacrylates (Fig. 1). A premature release of the active substances as a result of mechanical damage of the membrane may be a disadvantage of this system.

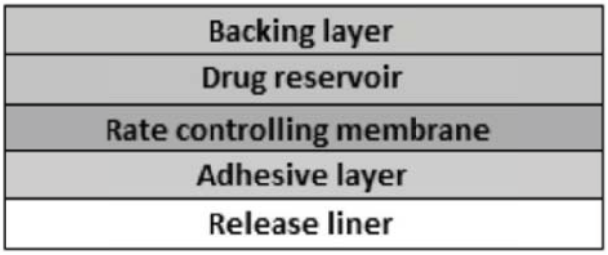


**Fig. 1.** Schematic of reservoir system [36]

**Matrix system**

Unlike the reservoir system, the release of an active substance is controlled by diffusion process. The drug is diffused in a hydrophilic or lipophilic polymer matrix (homogenous or multilayered). The release process of the active substance is controlled by lipophilicity and the structure of the matrix in TTS. The main advantage of this system is the impossibility of a sudden release of the active substance (as it happens in the case of reservoir system). In order to attach the patch to the skin, an adhesive layer is applied on the edge of the matrix (Fig. 2). It is not always necessary to apply the adhesive layer. Sometimes the matrix possesses adhesive properties itself.

**Micro-reservoir system**

This system is an indirect structure between the reservoir and the matrix system. A hydrophilic phase (40% solvent polyethyleneglycol in water) is dispersed in lipophilic phase, as a micro-reservoir, in which there is the active substance. The release process depends on many

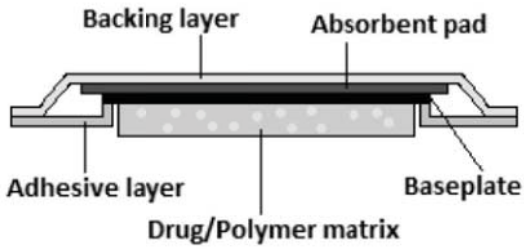


**Fig. 2. S**chematic of matrix system [36]

factors, e.g. diffusion rate in matrix, diffusion in a reservoir and its membrane or micro-reservoir/matrix ratio (Fig. 3).

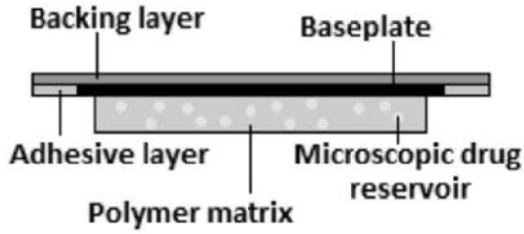


**Fig. 3.** Schematic of microreservoir system [36]

**Single-layer drug in adhesive system.**

This is the simplest form of TTS. The same material serves as an adhesive and a drug-containing layer. In this case, an adhesive layer has a double function. It is responsible for the adhesion to skin and for the release of a drug (Fig. 4). Using this type of patches is comfortable because they are thinner and smaller than others.

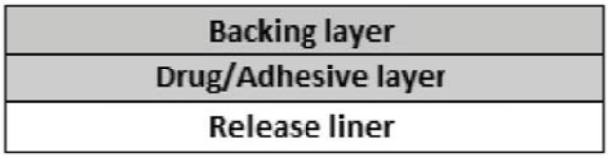


**Fig. 4.** Schematic of single-layer drug in adhesive system [36]

**Multi-layer drug in adhesive system**

In this case, the structure is similar to the one of a single-layer drug in the adhesive system. However, they differ in the number of adhesive layers. A multi-layer drug in the adhesive system provides a better control over the drug release than a single-layer drug in the adhesive system. The adhesive layers may not be composed of the same material and they are usually separated by a membrane (Fig. 5).

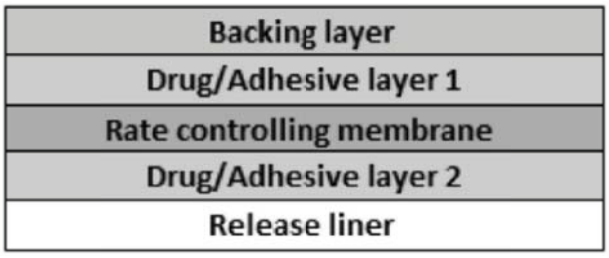


**Fig. 5.** Schematic of multi-layer drug in adhesive system [36]

## BREAKING THE BARRIERS OF DRUG PERMEATION THROUGH THE SKIN

To improve the efficiency of transdermal drug delivery system, the drug must be capable of penetrating the skin barrier and reach the target site. Passive systems are restricted to low-dosage lipophilic and low molecular-weight molecules (<500 Da). Higher molecular weight molecules (>500 Da) do not penetrate the stratum corneum [18,43].

**Table 1.** Therapeutic substances present in the commercial preparations of TTS and their uses [33]

| International drug name | Indications |
|---|---|
| Nitroglycerin (Glyceryl Trinitrate) | Prevention of angina pectoris due to coronary artery disease |
| Hyoscine (Scopolamine) | Prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery |
| Nicotine | Reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking |
| Fentanyl | Management of persistent, moderate to severe chronic pains |
| Buprenorphine | Chronic pain |
| Flurbiprofen | Muscle and joint pain |
| Diclofenac epolamine | Topical treatment of acute pain due to minor strains, sprains, and contusions |
| Clonidine | Treatment of hypertension |
| Estradiol | Treatment of vulvar and vaginal atrophy, and vasomotor symptoms associated with the menopause therapy of hypoestrogenism, prevention of postmenopausal osteoporosis |
| Estradiol, levonorgestrel | Menopause: vasomotor symptoms and osteoporosis prevention |
| Norelgestromin, ethinylestradiol | Prevention of pregnancy in women |
| Testosterone | Hypogonadism in damage to the testicles and the parts of the brain which control the release of testosterone |
| Lidocaine | Pain associated with post-herpetic neuralgia |
| Lidocaine, tetracaine | Local dermal analgesia |
| Oxybutynin | Treat symptoms of overactive bladder, incontinence |
| Methylphenidate | Treatment of Attention Deficit Hyperactivity Disorder (ADHD) |
| Selegiline | Treat major depressive disorders |
| Rivastigmine tartrate | Treatment of mild to moderate dementia of the Alzheimer's type and dementia associated with Parkinson's disease |
| Granisetron | Prevention of nausea and vomiting in chemotherapy |

The passive approach entails the optimization of formulation of drug vesicles. It can modify the permeability of the stratum corneum layer of the skin, which allows the delivery of higher molecular weight compounds. The chemical enhancers are called penetration enhancers, sorption promoters or accelerants. Penetration enhancers may include chemicals such as alcohols (ethanol), alkanols (decanol), azones (laurocapram), sulphoxides (dimethylsulphoxide), glycols (propylene glycol), pyrrolidones, surfactants, and terpenes [48,51].

Below, some of the important properties of the penetration enhancers are presented:

– they are non-toxic, non-irritating and non-allergenic,
– they present no pharmacological activity within the body,
– they are compatible with both the excipients and drugs,

– they work rapidly but the activity and duration of the effect should be predictable and reproducible,
– they deliver drugs into the body while preventing the loss of endogenous material from the body,
– barrier properties after removing from the skin should return rapidly and fully.

Passive approaches also include the use of pro-drugs, liposomes, and other vesicles [8].

Although passive methods do not sufficiently improve the permeation of drugs with molecular weights >500 Da, lots of the development efforts in transdermal drug focus on active systems of delivering a wider range of drug molecules, including oligonucletides, peptides, and proteins. The active methods include physical or mechanical methods of enhancing the delivery such as electroporation, iontophoresis, mechanical perturbation, ultrasound, and needless injection. [8].

One of the methods of enhancing transdermal drug delivery is electroporation, which consists of short, high-voltage electrical pulses [47]. This technique forms transient pores that enable skin penetration by the macromolecular drug substances. The efficacy of electroporation depends on various factors e.g. the applied voltage, duration, the number of pulses, and the physicochemical properties of drugs [1,46]. This method has been used in case of big molecules of different lipophilicity and sizes (proteins, peptides) [4,8].

Another method that uses an electric field is iontophoresis. Unlike electroporation, this technique uses a small electrical potential (0.5 mA/cm$^2$ or less ) afforded by constant current iontophoresis. The amount of the supplied active substances is directly proportional to the size of a charge passed [1,27]. This technique is used for drugs which are normally difficult to administer e.g. peptides and oligonucleotides [5].

Ultrasound technology is another method that can help increase skin permeation. Its usage in drug delivery through the skin is known as sonophoresis (phonophoresis). Two types of sonophoresis techniques can be distinguished: low frequency ultrasound (20–100 kHz) and therapeutic frequency ultrasound (1–3 MHz) [23]. However, this mechanism is not fully known. It is accepted that main factor is acoustic cavitation (growth, splitting or interaction of gas bubbles under the influence of the acoustic pressure oscillations in the solution) [38].

**Table 2.** Review of selected items from the literature with different active substances used in the research on TTS

| International drug name/active ingredient | Type of TTS/controlling release element | Class of drug | Indications/ drug action | Advantages |
|---|---|---|---|---|
| Silver nitrate (29) | Bio-patch: silver hybridized porous chitosan patch | Inorganic compound | Antibacterial activity, prevent infection of the wound | Biocompatible |
| Tulobuterol (TBR) (45) | Crystalline TBR distributed homogeneously in a matrix | Beta blocker | Bronchodilator, bronchial asthma | High permeability into the skin's keratin layer; controlled release rate |
| Desogestrel (44) | Matrix type patch, polyisobutylene with copovidone and mineral oil | Progestogen (new generation) | Contraception, ovulation and sperm penetration inhibition | Lack of drug leakage issues and ease of manufacturing, without causing undesirable crystallization |
| Paroxetine (17) | Liposomal gel transdermal patch (reservoir type) | Serotonin reuptake blocker | Antidepressant | Improvement the bioavailability (initial high plasma concentration after oral administration) |
| Diclofenac sodium (20) | Nanosilica/acrylic acid grafted guar gum membrane | Non-steroidal anti-inflammatory drug | Rheumatoid arthritis | Increased membrane stability, biocompatibility, reduction severe gastrointestinal and renal dysfunction |
| Diltiazem hydrochloride (7) | Multiwalled carbon nanotube with polyvinyl alcohol (membrane) | Calcium channel blockers | Treat hypertension, angina and certain heart rhythm disorders | High strength and elasticity membrane |
| Aloin (barbaloin) (52) | Liposomes immobilized in Layer-by-layer films with a polyelectrolyte | Anthraquinone from Aloe vera | Anti-inflammatory | Biocompatibility, preserve the activity of biomolecules for considerable periods times |
| Tenoxicam (2) | Proniosome gel formulation ("dry niosomes") | Non-steroidal anti-inflammatory drug | Long-acting non steroidal anti-inflammatory drug | Solving the problem of hydrophilic nature of the drug |
| Ondansetron (34) | Hydrogels: hydroxyethyl-cellulose or hydroxypropyl-cellulose with l-menthol (penetration enhancer) | Serotonin 5-HT3 antagonist | Treat nausea and vomiting associated with cancer chemotherapy, radiotherapy, anesthesia and surgery | Feasibility of delivering ondansetron transdermally |
| Insulin (11) | Insulin-loaded nanovesicles in combination with iontophoresis and microneedles | Peptide hormone | Diabetes therapy | Non-invasive delivery of peptides with large molecular weights |
| Sumatriptan (37) | Iontophoretic patch | Triptan | Treatment of migraine | Reduction of difficulty in taking oral medication (vomiting often accompanying migraine) |
| Vinpocetine (16) | Laurate sugar ester proniosomes (absorption and penetration enhancer) | Poorly water-soluble vincamine derivative | Treatment of disorders arising from cerebrovascular and cerebral degenerative diseases | High efficiency in systemic delivery together with lack of irritancy and excellent safety profile |
| Galantamine (35) | Pressure-sensitive-adhesive patch with oleic acid as enhancer | Alkaloid | First-line pharmacological agent for the treatment of Alzheimer's disease | Elimination cholinergically mediated gastrointestinal effects: nausea, vomiting, diarrhea, and anorexia |
| Morphine hydrochloride (MH) (24) | Polyethylene sponge foam impregnated with MH | Opioid analgesic | Management of moderate-to-severe pain in cancer and postoperative patients | Suggestion that transdermal morphine can be used for palliative care |
| Timolol maleate (15) | Different sugar fatty acid esters as permeation and absorption enhancer | Non-selective beta-adrenergic blocking agent | Treatment of hypertension, angina pectoris, myocardial infarction and glaucoma | Future use of sugar esters as promising absorption and penetration enhancer |
| Tolterodine (53) | Drug-in adhesive patches with O-acylmenthol as penetration enhancers | Anti-muscarinic | Treatment of urge incontinence | Transdermal delivery drug potential, the most promising enhancer, side effects elimination |
| Ranitidine (14) | Gel formulation, iontophoretic | Histamine $H_2$-receptor antagonist | Gastro-oesophageal reflux disease, benign gastric and duodenal ulcerations | Potential of transdermal iontophoresis |

Another way of enhancing transdermal drug delivery for big molecules is a micro-needle based device. This device combines the advantages of using hypodermic needles and TTS. This method does not cause an undesirable, excessive pain and tissue injury. Also, the control of the drug release is similar to the one where hypodermic needles are used. Micro-needles of various sizes, from sub-micron to millimeters, are made of silicon, metal, and polymer [19,28,32]. They create micron-sized pores that make the transport to the big macromolecules and even micro-particles possible [31]. Using micro-needle patches is particularly comfortable when a frequent administration of drugs is necessary (such as administration of insulin) [28].

In order to enhance drug permeation through the skin several enhancers are used in a single system. The combination of chemical and physical enhancement techniques has shown the synergistic effect in the permeation enhancement. It is recommended to choose a combination with different mechanisms of permeation enhancement. These combinations increase the safety of patch usage by preventing permanent and irreversible changes in the skin [9].

## THE FUTURE OF TTS TECHNOLOGY

Table 2 presents examples TTS technological solutions, which are currently in development.

## CONCLUSIONS

Due to numerous advantages of the Transdermal Therapeutic System, the issue has been the subject of many researchers' projects. An increasing number of new drug products are being developed for transdermal delivery. Despite some disadvantages, for example local irritation at the site of application, transdermal drug delivery is a good alternative to minimize the limitations related to oral and parenteral administration of drugs. The effectiveness of TTS system depends on the drug's ability to invade the skin barrier. In order to exploit the TTS more efficiently a number of scientists have been working on some combinational approaches to manufacturing TTS. Several new technologies are investigated to allow TTS to be transformed in the near future and offer even more benefits.

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