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A Review on Transdermal Drug Delivery Patches

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Human civilizations have used substances to the skin as cosmetic and therapeutic agents for thousands of years. The skin, on the other hand, was not exploited as a drug delivery method until the twentieth century. The term "transdermal" was first used in 1944 by Merriam Webster, indicating that it is a relatively new notion in medicinal and pharmacological practice. Transdermal medicines are doses that are self-contained and distinct. To produce a systemic effect, drugs are delivered through the skin. Without causing any changes in the drug's plasma concentration Topical application of medicinal medicines has a number of advantages. There are numerous advantages to this technique of drug delivery over traditional oral and invasive approaches. Also, ensure that the fluid is released in a regulated manner. A medication for a long amount of time. As a result, a variety of chemical and physical approaches to transdermal patch development are being investigated.

Keywords: Transdermal; permeation pathways; drug delivery; matrix; reservoir.

1. INTRODUCTION

Patches, also known as transdermal drug delivery system (TDDS), are dosage forms that deliver a therapeutically effective dose of medicine through the patient's skin. Transdermal distribution has a benefit over injection and oral delivery because it improves patient compliance and prevents first-pass metabolism [1] Since the first transdermal patch containing scopolamine was introduced in 1979, transdermal medicine administration has made a significant

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Table 1. Drug product and clinical use of transdermal patches on the current market [7]

Drug	Product name	Clinical use
Scopolamine	Transdermal-Scop	Motion sickness
Nitroglycerin	Transdermal-Nitro	Angina Pectoris
Clonidine	Catapres-TTS	High blood pressure
Estradiol	Estraderm	Menopause
Fentanyl	Duragesic	Chronic pain
Nicotine	Nicoderm	Smoking cessation
Testosterone	Testoderm	Testosterone low level
Lidocaine/epinephrine	Iontocaine	Pain relief
Estradiol/ Norethidrone	Combipatch	Menopause
Lidocaine	Lidoderm	Pain relief
Norelgestromin	Ortho Evra	Contraception
Estradiol/Levonorgestrel	Climara Pro	Menopause
Oxybutynin	Oxytrol	Overactive bladder
Selegiline	Emsam	Depression
Rivastigmine	Exelon	Dementia

contribution to medical practice, but it has yet to be recognized as a viable alternative to oral delivery and hypodermic injections [2] The improved patient compliance and effectiveness of a medicine delivery system are intimately related. For successful TDDS, the medication must be able to permeate the skin and easily reach the transdermal drug delivery technique has been around for quite some time [2] principle, transdermal patches are incredibly simple to use [3,4]. A high dose of medicine is administered the inside of the body. A patch that is worn for an extended period of time on the skin span of time A diffusion method is used to disperse the medicament directly into the bloodstream via the skin because the patch has a high concentration while the rest of the area has a low concentration, Due to its high concentration, the drug will continue to disseminate [5,4]. Maintaining a long time in the bloodstream. The drug's constant blood concentration [6]. In 1979, the US Food and Drug Administration (FDA) approved the first transdermal system containing scopolamine, and nicotine patches were allowed in 1984. Transdermal patches for pain treatment, analgesic activity, contraception, and hormone replacement therapy were approved and commercialized by the FDA a decade later, and advancement in this field continues to this day [7]. Patient's compliance, cheap cost, and controlled drug release are also advantages. The likelihood of skin irritation, macromolecular agents, and the inability to distribute ionic medications are all limitations of transdermal drug administration, and it is not ideal for patients in shock or with poor peripheral blood flow [2].

2. TYPES OF TRANSDERMAL PATCHES [6]

2.1 Single Layer Drug-in-adhesive Patches

A single layer of sticky polymer is used as a reservoir for medication dispersion in Fig. 1. Underneath the single layer lies a placed in the single polymer layer and attaches to it, then it is freed from the backing laminate layer that supports the drug reservoir. A single layer drug-in- adhesive transdermal patch containing Daytrana is an example of a single layer drug-in-adhesive transdermal patch. Methylphenidate

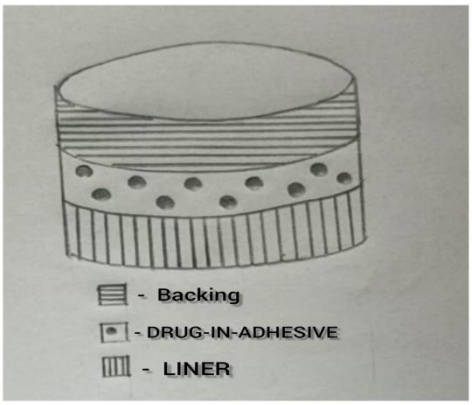

Fig. 1. Single layer drug in adhesive patch

2.2 Multilayer Drug-in-adhesive Patches [7]

Drug release is managed over a period of time in multilayer transdermal patches, which have a

drug reservoir layer and an adhesive layer. Multilayer system contain a temporary protective layer and a permanent backing laminate. Pain medication, smoking cessation treatments, and hormone therapy are all delivery via multilayer patches, with drug delivery lasting up to seven days.

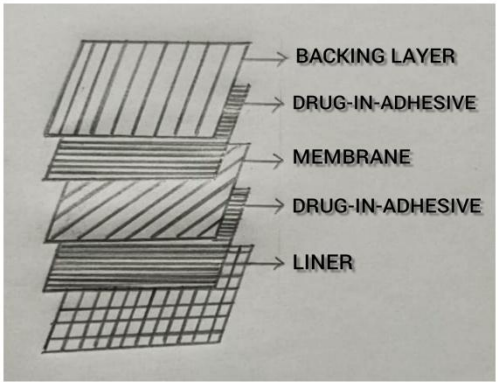

Fig. 2. Multi-layer drug in adhesive patch

2.3 Vapor Transdermal Patches

Vapor transdermal patches are made up of a single layer of sticky polymer that has a vapor release feature. On the market, there are a variety of various purposes. For instance, nicoderm is a type of nicoderm. CQ patches are nicotine vapor transdermal patches with essential oils that, when activated, release nicotine vapour. Can assist you in quitting smoking in 2007, this product was first launched to the European market. Another form of vapour patch that can be utilized in cases of decongestion altacura vapour patches, which included essential oils. There are also vapour patches that include antidepressant medications or sedatives on the market (Table 1).

2.4 Membrane Moderated Transdermal Reservoir Patches

A transdermal patch with a drug reservoir, an impermeable metallic plastic laminate backing layer, and a porous polymeric membrane that controls drug release over time. Polymeric materials (e.g., hypoallergenic) are used to create the membrane. Fig. 3 shows a Schematic diagram of several transdermal patches.

Ethylene vinyl acetate copolymer, genic sticky polymer). The drug is contained in a transdermal patch.

The drug's molecular dispersion in a polymer matrix, which is part of the preparation, is regulated [7]. Transdermal-Nitro containing nitroglycerin for one-day application, Transderm-Scop carrying scopolamine for three-day application, and Catapres containing clonidine for three-day application are example of commercial transdermal patches with modulated drug release. Application period of seven days (Table 1).

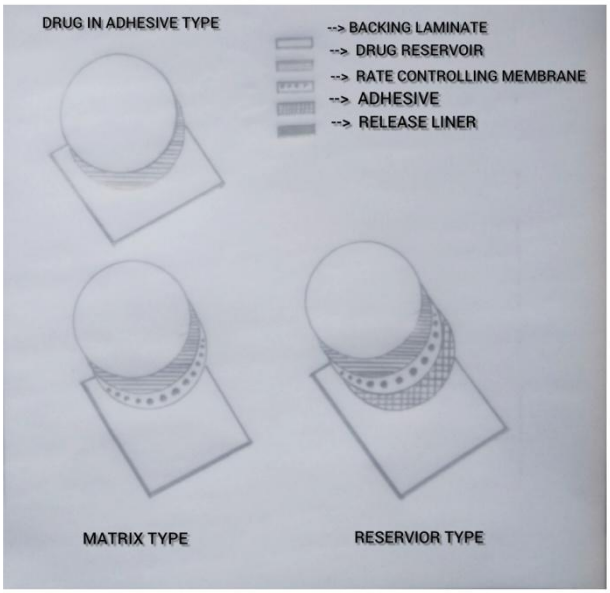

Fig. 3. Several transdermal patches

2.5 Micro Reservoir Transdermal Patches

Matrix dispersion and a drug reservoir re combined in micro reservoir transdermal patches. The reservoir is made by spreading the drug suspension on a lipophilic polymer after suspending it in an aqueous solution of hydrophilic polymer. A high shear mechanical force is used to disperse the material, resulting in the formation of thousands of microscopic, non-leachable spheres. The drug's release profile is based on a maintaining a constant drug level in the plasma at a zero order rate of kinetic drug release. Because the drug dispersion needs to be cross-linked, crosslinking polymeric agents are frequently added stable in terms of thermodynamics [8, 9].

2.6 Matrix System: Drug-in-adhesive

The drug reservoir is designed to distribute the dug on an adhesive polymer using single layer or multilayer transdermal patches, as shown in Fig. 1. The sticky polymeric components are melted or solvent cast onto an impermeable backing layer to form a drug-polymer matrix [10]. There are a variety of commercially available products of this type. The NicoDerm patch includes 100 micrograms of estradiol for a one-day application. The nicotine in the CQ transdermal patch can help you quit smoking for up to 10 weeks. (See Table 1.)

2.7 Matrix Systems: Matrix-dispersion

A hydrophilic or lipophilic polymer matrix serves as the reservoir in a matrix transdermal patch, and the drug is homogeneously disseminated in the matrix [11]. By putting the drug-polymer matrix over a plate with an impermeable laminate backing. Commercially available goods. Nitro-Dur, a matrix dispersion patch containing nitroglycerin and minitran, provides a continuous medication flow through undamaged skin (Table 1).

2.8 Miscellaneous Transdermal Patches

Transdermal patches with adhesive tapes, transdermal gel, transdermal spray, iontophoretic delivery, and phonophoresis delivery are all FDA-approved transdermal matrix delivery techniques, as illustrated in Table 2.

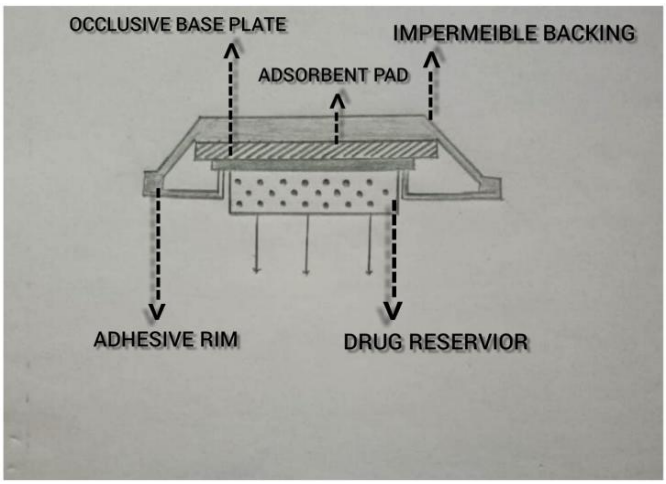

Fig. 4. Micro reservoir transdermal patches

Table 2. FDA approved other transdermal delivery systems

Drug	Product name	Transdermal delivery system
Flurandrenolide	Cordran Tape	Transdermal tape
Testosterone	AndroGel	Transdermal gel
Estradiol	Evamist	Transdermal spray
Fentanyl HCL	IONSYS	Transdermal patch
Insulin	Vyteris insulin patch	Iontophoretical patch
Hydrocortisone	Tegaderm patch	Electrophotophoresis

3. BIOPHARMACEUTICAL PARAMETERS IN TRANSDERMAL PATCH DRUG SELECTION [12]

1. The dose should be kept modest, around 20mg per day.
2. The half-life should be shorter than 10 hours.
3. The molecular weight of the compound should be 400.
4. Log P should be used as the partition coefficient. (Octanol water) in the range of 1.0 to 4.
5. The permeability coefficient of the skin should be 0.5X 10-3cm/h
6. The drug should not irritate or sensitive the skin in any way.
7. Bioavailability in the mouth should be low.
8. The therapeutic index should be as low as possible.

4. TRANSDERMAL PATCHES ARE NOT USED IN THE FOLLOWING CIRCUMSTANCES

When using a transdermal patch, avoid the following situations:

1. There must be a cure for acute pain.
2. In cases where a quick dosage is required it is necessary to do a titration.
3. When there is a need for a dose less than or equal to 30mg/24hr.

5. LIMITATIONS FOR TDDS SELECTION [13]

This method cannot be used to give all sorts of medications, the drug must have some attractive physicochemical characteristics.

1. Drugs that require high plasma levels are ineligible.
2. Drugs that cause skin irritation are not recommended.
3. Contact dermatitis is a type of dermatitis that occurs when someone comes
4. Drugs with a high molecular weight are not suited.
5. Not suited for medications that are broken down during metabolism.
6. The transmission of information through the skin
7. The transdermal method cannot be used for a significant number of people. Because the skin is such an effective barrier, for the purpose of drug penetration only a low dose can be used to administer.
8. The skin's barrier properties differ from the location to the next. From one person to the next, and from one person to the next also with the passage of time.

5.1 Therapeutic Applications of TDDS [14]

1. To promote adequate drug delivery, hisetal, which is used to treat multiple sclerosis, can be synthesized in TDDS with oleic acid as a permeability enhancer.
2. Non -steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac sodium and celecoxib may be formulated in TDDS to avoid the stomach lesions associated with oral dosage.
3. Drugs with a short biological half and significant first pass metabolism, such as captopril, verapamil, terbutalinesulphate, pinacidil, and propranolol, that are used for long term dosage in chronic conditions, can be manufacture as TDDS to obtain prolonged steady state plasma concentration.
4. Drug release may be accelerate using hydrophilic polymers like polyvinylpyrrolidone, while drug delivery may be delayed with hydrophobic polymers like ethyl cellulose.
5. The use of a gel formulation with a betahistine lipid dispersion system could lead to the creation of an effective controlled release transdermal system.

6. ADVANTAGES OF TDDS

This approach delivery offers many advantages over traditional methods;

1. As a substitute for the oral route,
2. Transdermal medication administration avoids the difficulties of gastrointestinal absorption, including enzymatic and pH issues.
3. Deactivation of the linked genes.
4. This strategy also enables for cost savings. Due to the shortened pharmacological dosing First-pass metabolism is avoided.
5. In order to avoid gastro intestinal incompatibility, you should eat foods that are compatible with your digestive system.

6. Activity that is predictable and has a long duration.
7. Keeping unfavorable side effects to a minimum [2,15]

7. DISADVANTAGES OF TDDS: [16]

1. At the moment, only tiny lipophilic medicines can be given through the skin.
2. The drug molecule must be powerful because the patch size restricts the amount of medication that may be given.
3. Its not recommended for high-dosage medications.
4. Adhesion varies depending on the patch type and the surrounding environment.
5. Adhesion varies depending on patch type and environmental factors.
6. Irritation and hypersensitivity reactions to the skin are possible.The skin's barrier functions vary from one location to the next on the same individual, from person to person, and with age.

8. EVALUATION TEST OF TRANSDERMAL PATCH

8.1 Drug Excipients Interaction Studies [17]

To make a good product, the drug and excipients must be compatible. Stable product, therefore it is essential to uncover any potential flaws. Interplay of physical and chemical forces Interaction studies are a type of research that looks at how people interact Thermal analysis is widely used in this process. FT-IR by contrasting UV and chromatographic methods assay, melting, and other physiochemical wave numbers maxima etc. [18]

8.2 Drug Content [19, 20]

A portion of the patch must be dissolved in a certain volume of a suitable solvent. After that, the solution will be filtered using a filter medium. Using the appropriate technology (UV or X-rays), determine the drug's content. Method of HPLC). The average of three values is represented by each value samples.

8.3 Weight Uniformity [21, 22]

The manufactured patches must be dried in order to achieve weight uniformity. Before testing at 60˚C for 4 hours Patching in a specific region needs to be cut and weighed in different portions of the patch balance of the digital the mean and standard deviation of the average weight Individual weight must be used to determine value.

8.4 Patch Thickness

The average thickness and width of the drug-loaded patch are determined by measuring the thickness of the patch at several spots with a digital micrometre. Standard deviation for the same, in order to verify that the thickness of the patch that has been prepared [21]

8.5 Moisture Loss

Weight the produced films individually and store them at 40˚C in a desiccator containing calcium chloride. The films are gonna be shown after 24 hours. Reweigh and calculate the moisture loss percentage from the formula below [13]

$$\% \text{ Moisture Loss} = [\text{Initial wt} - \text{Final wt}] \times 100$$

8.6 Swellability [22]

The 3.14 cm2 patches were weighed and placed in a petri dish with 10 ml of double distilled water, where they were allowed to imbibe. An increase in the weight. The patch was selected at predetermined interval until a conclusion was reached. It was discovered that the weight was constant.

The swelling degree (S) was computed using the formula,

$$S(\%) = Wt\text{-}Wo/Wo \times 100$$

Where S is percent swelling, Wt is the weight of patch at time t and Wo is the weight of patch at time zero.

8.7 In- vivo Studies [17]

In- vivo studies are the most accurate representation of a drug's performance. Variables that cannot be cinsidere in in-vitro investigations can be completely considered. In-vivo research have been looked into. In vivo testing of the following methods can be used to perform TDDS: Models based on animals Volunteers from the human race

8.8 Models of Animals

The most commonly utilized animal species for testing Transdermal medication delivery system are used in mice, hairless rats, and other animals. A hairless dog, a hairless rhesus monkey, a rabbit, and a guinea pig are all examples of hairless animals etc.

8.9 Human Models

The collecting of human models is the final step in the creation of a transdermal device of pharmaceutical pharmacokinetics and following the administration of the patch, pharmacodynamics data a group of human volunteers Clinical trial have been done to determine efficacy, risk, side effects, and patient compliance, among other things.

8.10 Stability Studies

It is necessary to undertake stability studies by storing the TDDS in accordance with ICH rules. For 6 months, sample were kept at 40.5% RH and 40.5% C. At 0, 30, 60, 90 and 180 days, sample were taken. Analyze the medication content appropriately [21, 24].

9. RECENT ADVANCES IN THE FIELD OF TRANSDERMAL PATCHES [25, 26]

Protein delivery via patch technology: Large Protein transdermal delivery is a novel and intriguing delivery technology. There isn't any currently available commercial technologies. Proteins are incorporated into transdermal patches. TransPharma makes use of a one-of-a-kind printed patch. Technique for protein transdermal delivery as a result, its viadermdelivery is enhanced technology. These printed patches have precise protein dosage in a dry state its true. It was hypothesis that the extremely water soluble the interstitial fluid dissolves proteins. That is produced by the skin and secreted through the RF Micro Channels, making a very efficient network in situ concentration of protein solution the dissolved molecules are then delivered. Carried achieved through the use of RF Micro Channels in the skin's vital tissues, diffusing across a gradient of concentration.

Transdermal patches for diabetic monitoring that are painless [19, 27] the initial prototype patch is roughly 1cm in length and is constructed of polymers and thin metallic sheets are used in this projects. The 55th percentile it's easy to view the sample array. As well as their linkage made of metal when the sea is broken, the interstitial fluid, as well as the biomolecules included within, the biomolecules contained within it is possible to reach it via the skin's surface. Utilizing incorporated into the design are micro heating components. The structural layer of the patch nearest to the skin on the surface, a high-temperature heat pulse can be formed. Localized treatment that allows the stratum corneum to be pierced. During this process, the skin's surface is ablated. 30 milliseconds.

9.1 Technology and Approaches for the Future

Thermal poration is the process of creating water channels across the stratum corneum using heat. This method, know as pulsed heat, has been used to give traditional medications and to extract Glucose levels in human intestine fluids [19, 28].

Jet injectors are getting a lot of attention these days. Nowadays, which is allowing for betterment Design of a needle-free, regulated device medication solution are injected under the skin and further into the tissue.

A few millimeters into the skin, a little needle is placed. The skin and medication solution are pumped through the tube. A regulated pace of insertion of a needle into the skin. A micro infusion pump is a pump that is built into a device. Morphine has been applied to the skin in a large patch. This method was used to distribute to humans.

10. CONCLUSION

TDDS technology is widely recognized as the creation of a mass delivery methodology, making it the dominant medication injection mechanism for transdermal delivery across all skin types. While avoiding first-pass metabolism and other sensitivity issues associated with various drug administration routes Drugs can be found in a variety of devices and TDDSs. Be transported to the systemic circulation through the skin Drugs are normally given in a reliable and safe manner. TDDS is biochemically safe and stable until it reaches the target tissue. TDDS is a noninvasive, no allergenic treatment with a predetermined time and dose. Method of distribution that allows for uniform dispersion of medications at controlled and authorized doses.

There are numerous fresh additions and existing formula are in the process of being improved bioavailability of low-absorption drugs via easy routes of administration that allow large doses to be given over a lengthy period of time. As a result, the TDDS technology is fast gaining traction in the pharmaceutical industry. It has succeeded in acquiring major market value as a formulation method that can increase drug administration through topical channels for biomedical applications. However, despite decades of investigation, passive approaches such as chemical enhancers have remained unproven. Increased transdermal transfer only to a limited extent tiny molecules and have only had a mediocre success rate ability to improve macromolecule transport under adverse conditions. Clinically acceptable condition are possible [9]. The transdermal delivery efficiency of active transport systems involving external devices has grown significantly macromolecules and drugs. However, these technologies' ability to efficiently distribute medications is hampered by their reliance on electronic control systems that demand energy, limiting their usability and effectiveness cost. Procedures for piercing micron-sized pores in the skin micro needles, for example, can dramatically increase the transdermal administration of medicines, macromolecules, or particles is possible, but additional research is needed. Safety/minimal skin injury, as well as cost-effectiveness. The scale of TDDS in the domestic and international market for medication delivery systems has grown validated by a growing number of research reports and patents. Many companies and research organisations have commercially available products. Microneedlesae also gaining popularity among TDDS modalities, since they complement the limits of existing easy application and patch type needles and combine the benefits of microneedles to get higher results. Treatment efficacy and outcomes Manufacturing is required for this. While strategies for commercialization are being developed, prudent application of cutting-edge technology 3D bioprinting, for example. These TDDSs could benefit from advancements given the impetus for reducing the occurrence of cardiovascular aand central nervous system disorders, Diabetes, neuromuscular illnesses, hereditary diseases, and others are only a few examples contagious and localized infectious disorders, while also spearheading vaccine advancements and providing patient support. For long-term use, self-administration of medicines is preferred treatment.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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