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(REVIEW ARTICLE)

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# A review on transdermal drug delivery system

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## Abstract

In order to produce systemic effects, transdermal drug delivery systems (TDDS), commonly referred to as "patches," are dosage forms that are intended to spread a therapeutically active amount of medicine across the skin of a patient. Drugs that are applied topically are delivered using transdermal drug delivery devices. These are pharmaceutical preparations of varying sizes, containing one or more active ingredients, intended to be applied to the unbroken skin in order to deliver the active ingredient after passing through the skin barriers, and these avoid first pass metabolism. Today about 74% of drugs are taken orally and are not found effective as desired. To improve efficacy transdermal drug delivery system was emerged. In TDDS the drug easily penetrates into the skin and easily reaches the target site. To get around the problems with medicine delivery via oral route, transdermal drug delivery systems were developed. These systems have been utilized as secure and reliable drug delivery systems since 1981.

**Keywords:** Transdermal drug delivery system; Patch; Topical administration; Systemic circulation

## 1. Introduction

Transdermal drug delivery is a painless method of delivering drugs systemically by applying a drug formulation onto healthy skin. The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer [1,2]. TDDS is an integral part of novel drug delivery system and it was a tenth century when the skin was used as administration site for long term drug delivery. Transdermal drug delivery is the one of the most reliable as well as effective technique. Transdermal route has become one of the most successful and innovative drug delivery systems [3]. This system was first introduced more than 20 years ago. The technology generated tremendous excitement and interest amongst major pharmaceutical companies in the 1980's and 90's. By the mid to late 1990's, the trend of Transdermal drug delivery system companies merging into larger organizations [4]. In this approach, patches that are topically applied medications distribute medications for systemic effects at a predetermined and controlled rate. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders [5]. In addition to increasing the efficacy and safety of the treatment, developing a novel delivery mechanism for current therapeutic molecules also increases patient compliance and overall therapeutic benefit to a significant extent [6]. More recently, such dosage forms have been developed and modified in order to enhance the driving force of drug diffusion (thermodynamic activity) and to increase the permeability of the skin. These approaches include the use of penetration enhancers, supersaturated systems, hyaluronic acid, pro-drugs, liposomes and other vesicles [7]. By boosting patient compliance and eliminating first pass metabolism, transdermal administration offers a competitive advantage over injectables and oral methods. Transdermal delivery not only allows for continuous, regulated drug administration but also removes pulsed systemic circulation for medicines with short biological half-lives, which often causes undesirable side effects. Thus, various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc [8].

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Atorvastatin (Lipitor and Torvast), Fluvastatin (Lescol), Lovastatin (Mevacor, Altocor, Altoprev), Pitavastatin (Livalo, Pitava), Pravastatin (Pravachol, Selektine, Lipostat), Rosuvastatin (Crestor), and Simvastatin (Zocor, Lipex) are some of the statins available. At present, these statins are administrated orally on a daily basis. All statins are absorbed rapidly by oral administration; however, several problems have been found associated with the daily oral administration. For instance, Atorvastatin provides a bio-availability not more than 14% and only about 5% of Simvastatin enters into the general circulation. This is due to the first-pass metabolism in the liver and the clearance by the digestive system [9]. Transdermal delivery systems are currently available containing Scopolamine (Hyoscine) for motion sickness, Clonidine and Nitro-glycerine for cardiovascular disease, Fentanyl for chronic pain, Nicotine to aid smoking cessation, Estradiol (alone or in combination with Levonorgestrel or Norethisterone) for hormone replacement and testosterone for hypogonadism. Despite the small number of drugs currently delivered via this route, it is estimated that worldwide market revenues for transdermal products have shares in USA at 56%, Europe at 32% and Japan at 7%. In a recent market report, it was suggested that the growth rate for transdermal delivery systems will increase 12% annually through to 2007[10].

In 1979, the FDA authorized Transderm SCOP, the first transdermal device, to treat travel-related motion sickness and nausea. The majority of transdermal patches are made to release the active component slowly for several hours to days after being applied to the skin. This is especially advantageous for prophylactic therapy in chronic conditions [11].

## 2. Definition of Transdermal Patch

It is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream in controlled manner to show therapeutic effect.

**Figure 1** Transdermal Patch

### 2.1. Advantages of Transdermal drug delivery System

- Dose frequency can be reduced.
- Drug concentration can be reduced due to improved bioavailability.
- First pass metabolism by liver can be escaped.
- They can prevent gastrointestinal medication absorption issues caused by stomach pH, enzymatic activity, and drug interaction with food, drink, and other orally administered pharmaceuticals.
- Reduced plasma concentration levels of drugs, with lower side effects.
- They prevent the hassle of parenteral therapy because they are non-invasive.
- They improved compliance compared to previous dosage forms that required more frequent dose administration because they offered longer therapy with a single application.
- Drug therapy may be terminated rapidly by removal of the application from the surface of the skin
- Self-administration is possible with these systems
- It reduces systemic drug interactions
- It offers longer duration of action

### 2.2. Disadvantage of Transdermal Drug Delivery System:

- Only potent drugs are suitable for transdermal delivery.

- Skin irritation may occur in some patient at the site of application
- This system is uneconomic
- Binding of the drug to the skin may cause dose dumping
- It can be used only for chronic conditions not for acute condition because chronic condition require drug therapy for a long period of time e.g., hypertension, angina and diabetes, etc.
- Therapeutic efficacy of the medicament can be affected by Cutaneous metabolism
- Ionic drugs are not suitable for Transdermal therapy.
- Suitable for Drugs with lesser molecular weight i.e., less than 500 Daltons

*Limitations of TDDS*

- Limited skin permeability
- Restricted to potent drugs
- Not suitable for large molecules i.e., above 500 Daltons
- Adhesion of the patch to the skin
- Drug may undergo degradation in the skin
- Drugs that are highly melting cannot be given by this route due to their low solubility both in water and fat
- Not at all suitable if they cause irritation to skin.
- This system cannot deliver ionic drugs.

**2.3. Anatomy and physiology of Skin**

Skin is the largest organ of the body, with a total area of about 20 square feet. Skin protects us from microbes and the elements, helps in regulation of the body temperature, permits the sensations of touch, heat and cold

Human skin consists of three well defined but mutually dependent tissues:

- The stratified, vascular, cellular epidermis
- Underlying dermis of connective tissues and
- Hypodermis.

*2.3.1. Epidermis*

The multi-layered epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Epidermis has outer stratum corneum and viable epidermis.

*2.3.2. Stratum corneum (Horney layer)*

This is the outermost layer of skin also called as Horney layer. It is approximately 10 μm thick when dry, but swells to several times this thickness when fully hydrated. It has 10 to 30 layers of dead, keratinized cells called corneocytes. The stratum corneum can be penetrated by drug molecules in one of three ways. Depending on the physicochemical characteristics of the medicine, the drug can be absorbed via the skin in a variety of ways. Drugs that are hydrophilic and lipophilic are absorbed via various pathways.

- Transcellular route
- Intercellular route
- Trans follicular route

*2.3.3. Viable epidermis*

This is situated beneath the outermost layer and varies in thickness ranging from 0.06 mm on the eyelids sole up to 0.8 mm on the palms. Going inwards, it consists of various layers as stratum granulosum, stratum lucidum, stratum spinosum and the stratum basal. In the basal layer, mitosis divisions of the cells constantly reproduce the epidermis and this proliferation compensates the loss of dead Horney cells from the skin surface.

*2.3.4. Dermis*

Dermis is 3 to 5mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerves. The control of body temperature relies heavily on the cutaneous blood supply. While removing pollutants and waste, it also gives the skin nutrition and oxygen. Most molecules that penetrate the skin barrier sink in capillaries, which are located 0.2 mm from the skin's surface. Thus, the blood supply maintains a very low dermal concentration of a permeant, and the ensuing concentration gradient across the epidermis is crucial for transdermal penetration.

*2.3.5. Hypodermis*

The dermis and epidermis are supported by the hypodermis, often known as subcutaneous fat tissue. It functions as a place to store fat. This layer offers nutrient support, mechanical protection, and aids in temperature regulation. It connects the body's major blood vessels and nerves to the skin and may contain organs that detect pressure.

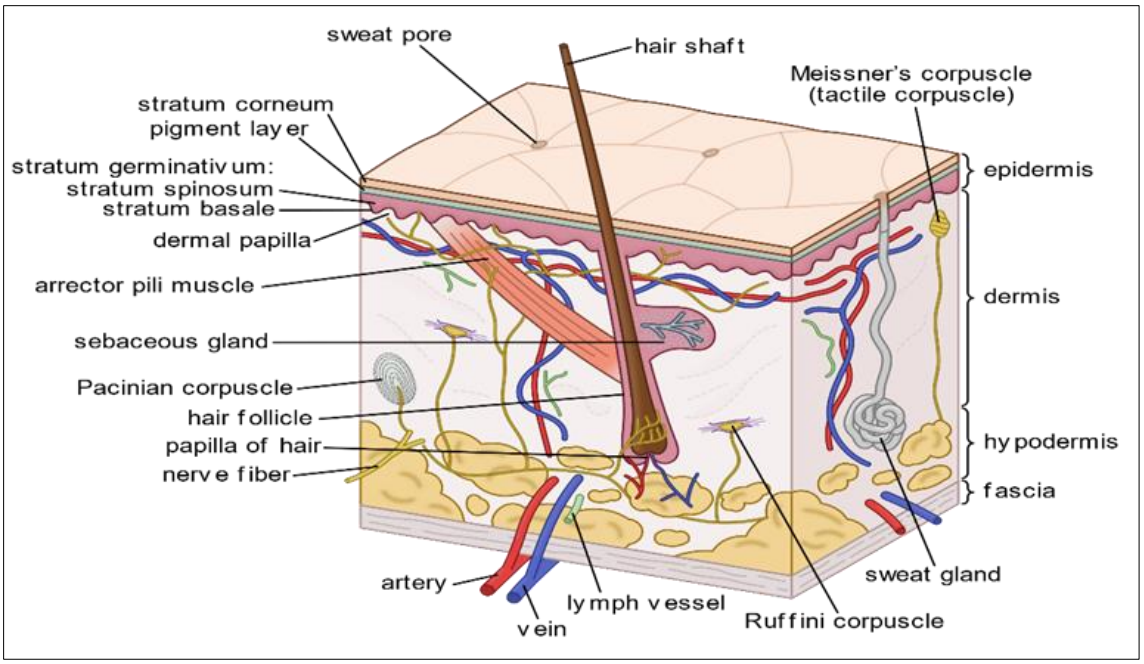


**Figure 2** Structure of Skin

## 2.4. Types of transdermal patches

- Single-layer drug-in-adhesive.
- Multi-layer drug-in-adhesive.
- Reservoir.
- Matrix.
- Vapour patch.

*2.4.1. Single-layer Drug-in-Adhesive*

It is distinguished by the medicine being included right inside the skin-contacting glue. In this transdermal system design, the adhesive doubles as the basis for the formulation, holding the medicine and all excipients in one backing film while simultaneously serving as a means of attaching the system to the skin. This type of system's medication release rate is influenced by how quickly the drug diffuses through the skin [12,13].

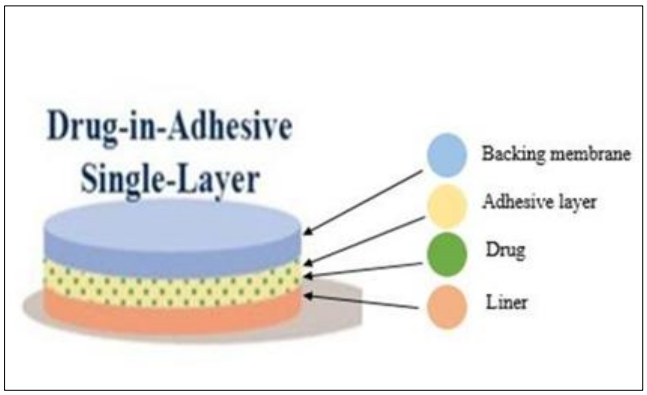


**Figure 3** Single layer Patch

*2.4.2. The Multi-layer Drug-in-Adhesive*

It is similar to the Single-layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive. The term "multi-layer" refers to the addition of either a membrane or numerous drug-in-adhesive layers underneath a single backing film in between two separate drug-in-adhesive layers. [12,13].

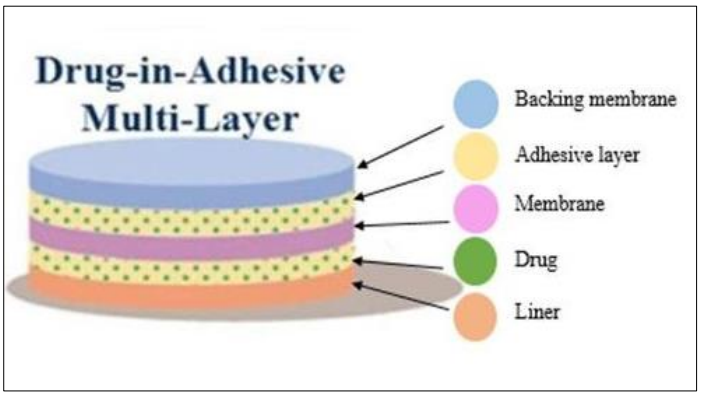


**Figure 4** Multilayer patch

*2.4.3. Drug Reservoir-in-Adhesive*

It is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. Either a continuous layer between the membrane and the release liner or a concentric design surrounding the membrane can include the adhesive component of the product that is responsible for skin attachment. [12,13].

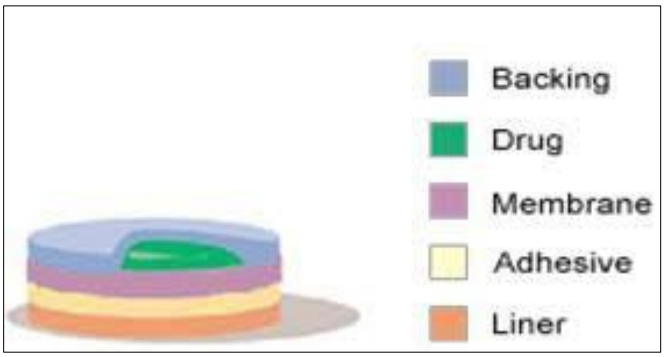


**Figure 5. Reservoir patch**

*2.4.4. Drug Matrix-in-Adhesive*

It is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix.[12,13].

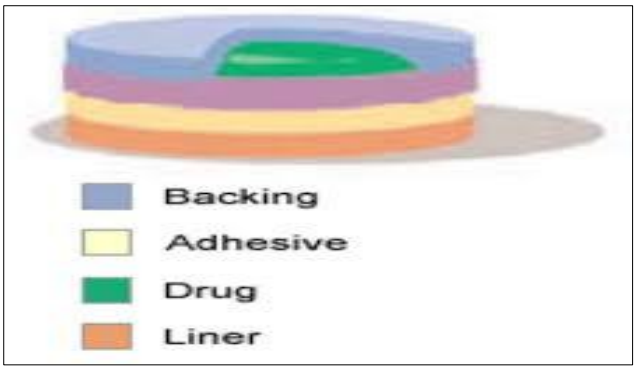


**Figure 6** Matric patch

*2.4.5. Vapour Patch:*

In this type of patch, the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The market is just starting to see the introduction of vapour patches, which may release essential oils for up to 6 hours. The vapour patches, which mostly treat decongestion instances, release essential oils. Controller vapour patches, which enhance sleep quality, are available as alternatives. There are also vapour patches on the market that can cut down on how many cigarettes a person smokes each month. Month are also available on the market [14].

*2.4.6. Components of TDDS*

The major components of a transdermal patch are:

Release Liner

Protects the patch during storage. The liner is removed prior to use [15].

Drug reservoir

The most important part of TDDS is drug reservoir. It consists of drug particles dissolved or dispersed in the matrix. Various Solvents and cosolvents are used to make the drug soluble. The effect of solvent and cosolvent should be considered while doing selection [15].

Adhesive

Serves to adhere the patch to the skin as well as the patch's component parts together. The adhesive must possess sufficient adhesion property so that the TDDS should remain in place for a long time. Pressure sensitive adhesives are commonly used for transdermal patch to hold the skin. Commonly used adhesives are silicone adhesives, poly iso butylene's adhesives and poly acrylate-based adhesives [15].

Membrane

Membrane controls the release of the drug from the reservoir and multi-layer patches. It may or may not contain rate-controlling membrane. It should be flexible enough not to split or crack on bending or stretching. Some of rate-controlling membranes are polyethylene sheets, ethylene vinyl acetate copolymer and cellulose acetate [15].

Backing

Shields the patch from the outside world. The backing layer should be impermeable to drug and penetration enhancers. It serves a function of holding the entire system and protects drug reservoir from atmosphere. The commonly used backing materials are polyesters, aluminized polyethylene terephthalate and siliconized polyethylene terephthalate [15].

## 2.5. Various methods for preparation TDDS

### *2.5.1. Asymmetric TPX membrane method*

A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX poly (4-methyl-1-pentene) asymmetric membrane, and sealed by an adhesive [16].

### *2.5.2. Circular Teflon mould method*

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butyl phthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular Teflon mould. The moulds are to be placed on a levelled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored for another 24 hrs at 25±0.5°C in a desiccator containing silica gel before evaluation to eliminate aging effects. The type films are to be evaluated within one week of their preparation [17].

### *2.5.3. Mercury substrate method*

25 In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 minutes to produce a homogenous dispersion and poured in to a levelled mercury surface, covered with inverted funnel to control solvent evaporation [18].

### *2.5.4. By using IPM membranes method*

*26 In this method drug is dispersed in a mixture of water and propylene glycol containing* carbomer 940 polymer and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane [19].

### *2.5.5. By using EVAC membranes method*

In order to prepare the target transdermal therapeutic system, 1% Carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; Carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device [20].

### *2.5.6. Aluminium backed adhesive film method*

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custam made aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks [21].

### *2.5.7. Preparation of TDDS by using Proliposomes*

The proliposomes

0 are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70°c temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20- 30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5 ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5 ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders proliposomes) are placed in a desiccator overnight and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization [22,23].

*2.5.8. By using free film method*

Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the Petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution [24].

*2.5.9. Simple Method of Preparing Transdermal Patches*

Method of preparation of TDDS was summarized by modifying the earlier reported methods. The patches were prepared by solvent casting method. The polymer (for example PVP/HPMC) was taken in a beaker with a minimum quantity of the solvent. Then 2/3rd of the solvent was mixed with the other polymers (for example PVA) and was added firstly with stirring at lower rpm and later at a higher speed. The plasticizer was added and homogeneously mixed and the drug was included with enduring agitation and the volume was made up. The films were cast onto a suitably designed and fabricated glass mould and then dried in oven at $40^0$C. The films were removed by using sharp blade by inserting along the edges of the film. The dried films were wrapped in butter paper and stored in a closed container away from light and in cool place [25,26].

**2.6. Applications of TDDS**

- The highest selling transdermal patch in the United States of America is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking. The first commercially available vapour patch to reduce smoking was approved in Europe in 2007.
- Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form, fentanyl CII (marketed as Duragesic) and buprenorphine CIII (marketed as BuTrans).
- Hormonal patches:
    - Oestrogen patches are sometimes prescribed to treat menopausal symptoms (as well as post-menopausal osteoporosis) and to transgender women as a type of hormone replacement therapy.
    - Contraceptive patches (marketed as Ortho Evra or Evra) and
    - Testosterone CIII patches for both men (Androderm) and women (Intrinsa).
- Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.
- Transdermal scopolamine is commonly used as a treatment for motion sickness.[43]
- The anti-hypertensive drug clonidine is available in transdermal patch form.[44]
- Emsam, a transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant approved for use in the U.S. in March 2006.[45]
- Daytrana, the first methylphenidate transdermal delivery system for the treatment of attention deficit hyperactivity disorder (ADHD), was approved by the FDA in April 2006.[27]
- Secuado, a transdermal form of the atypical antipsychotic asenapine, was approved by the FDA in October 2019.[28]
- Vitamin B12 may also be administered through a transdermal patch. Cyanocobalamin, a highly stable form of vitamin B12, is compatible with transdermal patching.[29]
- 5-Hydroxytryptophan (5-HTP) can also be administered through a transdermal patch, which was launched in the United Kingdom in early 2014.[30]
- Rivastigmine, an Alzheimer's treatment medication, was released in patch form in 2007 under the brand name Exelon.[31]
- In December 2019, Robert S. Langer and his team developed and patented a technique whereby transdermal patches could be used to label people with invisible ink in order to store medical information subcutaneously. This was presented as a boon to "developing nations" where lack of infrastructure means an absence of medical records. The technology uses a "quantum dot dye that is delivered along with a vaccine".[32]
- Caffeine patches, designed to deliver caffeine to the body through the skin. (33)

### 2.7. Adverse events

- In 2005, the FDA announced that they were investigating reports of death and other serious adverse events related to narcotic overdose in patients using Duragesic, the fentanyl transdermal patch for pain control. The Duragesic product label was subsequently updated to add safety information in June 2005.[34]
- In 2007, Shire and Noven Pharmaceuticals, manufacturers of the Daytrana ADHD patch, announced a voluntary recall of several lots of the patch due to problems with separating the patch from its protective release liner. Since then, no further problems with either the patch or its protective packaging have been reported. (35)
- In 2008, two manufacturers of the fentanyl patch, ALZA Pharmaceuticals (a division of major medical manufacturer Johnson & Johnson) and Sandoz, subsequently issued a recall of their versions of the patch due to a manufacturing defect that allowed the gel containing the medication to leak out of its pouch too quickly, which could result in overdose and death. As of March 2009, Sandoz—now manufactured by ALZA—no longer uses gel in its transdermal fentanyl patch; instead, Sandoz-branded fentanyl patches use a matrix/adhesive suspension (where the medication is blended with the adhesive instead of held in a separate pouch with a porous membrane), similar to other fentanyl patch manufacturers such as Mylan and Janssen. (36,37)
- In 2009, the FDA announced a public health advisory warning of the risk of burns during MRI scans from transdermal drug patches with metallic backings. Patients should be advised to remove any medicated patch prior to an MRI scan and replace it with a new patch after the scan is complete.[38]
- In 2009, an article in Europace journal detailed stories of skin burns that occurred with transdermal patches that contain metal (usually as a backing material) caused by shock therapy from external as well as internal cardioverter defibrillators (ICD) (39)

## 3. Conclusion

The transdermal drug delivery system (TDDS) review articles offer useful insights on the transdermal drug delivery systems and its evaluation procedure as a handy reference for the research scientist working on TDDS. The information above demonstrates that TDDS have significant potentials, since they can be used to create promising deliverable medications from both hydrophobic and hydrophilic active substances. More knowledge of the various biological interactions and polymer mechanisms is needed to optimise this drug delivery technology. The next generation of drug delivery systems, TDDS, has a realistic, practical use.

## Compliance with ethical standards

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*Disclosure of conflict of interest*

All the authors declare no conflict of interest.

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