WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Review on Transdermal Patches

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DOI: https://doi.org/10.55248/gengpi.2022.3.10.60

ABSTRACT

Since the start of life on the earth, humans have applied plenty of substances to their skin as cosmetics and therapeutic agents. However, it was the 20 th century once the skin became used as route for future drug delivery.Today about two third of drugs (available in market) are taken orally, but these aren't as effective as required. To enhance upon the features the transdermal drug Delivery system was emerged. Amongst all techniques that transdermal drug delivery systems (TDDS), also referred to as "patches," are dosage forms designed to deliver a therapeutically effective quantity of drug across a patient's Skin. It give controlled continuous delivery of drugs via the skin to the systemic circulation. Advantage of transdermal drug delivery system are limitation of hepatic first pass metabolism, improvement of therapeutic potency and maintenance of steady plasma level of the drug. transdermal patch (Skin Patch) uses a special membrane to control the rate At which the liquid drug contained in the reservoir within the patch will pass through the skin and Into the bloodstream. Drugs administered through skin patches include scopolamine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to stop osteoporosis after menopause), nitroglycerin (for angina), and lidocaine to relieve the pain of shingles (herpes zoster).Transdermal patches were developed in the 1970s and the first was approved by the FDA in 1979 for the treatment of motion Sickness. IN 1981, patches for nitroglycerin were approved, and today there exist variety Of patches for drugs such as clonidine, fentanyl, Lidocaine, nicotine, nitroglycerin, estradiol, Oxybutinin, scopolamine, and testosterone. There are combination patches for Contraception, also as hormone replacement. Depending on the drug, the patches typically last from 1to7days. Non-medicated patch markets include Thermal and cold patches, nutrient patches ,skin care patches. Skin patch uses a special membrane to manage the rate at which the liquid drug contained in reservoir within patch will pass through the skin and into the bloodstream. Some drugs should be combined with substances, such as alcohol, that increase their ability to penetrate the skin so as to be used in skin patch. From last twenty years over thirty five transdermal products are approved generating sale of $3.2 billion in 2002,which is predicted to rise to $4.5 billion in 2008. TDDS are adhesive drug-containing devices of defined surface area that deliver predetermined quantity of drug to the surface of intact skin at a programmed rate to reach the systemic circulation. The greatest challenge for transdermal delivery is that only a limited number of medicine are able to administration by this route.Tansdermal route of administration is reflected as one of the potential route for The local and systemic delivery of drugs. Transdermal patches provides better therapeutic effect with minimum facet effects transdermal patches are designed to release the active ingredient at a zero order rate for a period of several hours to days following application to the skin.

Keywords : Transdermal patch, drug delivery, Evaluation, Skin permeation

Skin and drug penetration

Anatomically, the skin can be divided into 2 layers: epidermis and dermis or corium [figure1], penetrated by Hair shafts and gland ducts. The skin is the most extensive organ of the human body, covering an area of about 2 m2 In an average human adult. The main skin layers, From inside to outside, include the fatty subcutaneous Layer (hypodermis), the dermis of connective tissue and the Stratified avascular cellular epidermis. This multilayered Organ receives about one-third of all blood Circulating

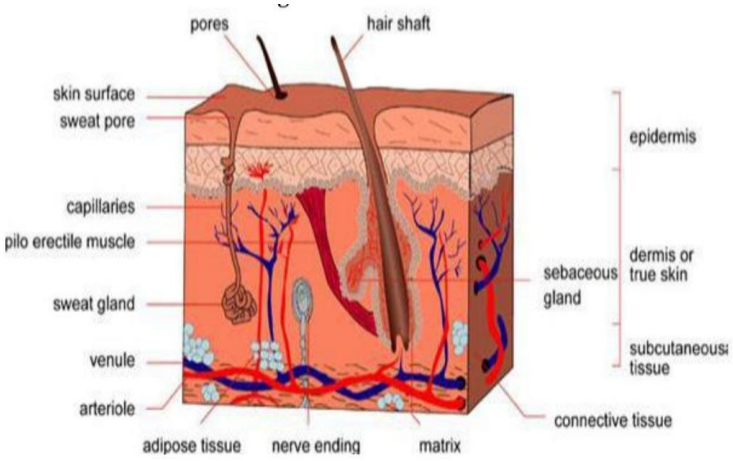


Figure 1 : Structure of Skin[12]

Through the body. The subcutaneous layer (SC) consist Of 15–20 layers of keratin filled corneocytes (terminally differentiated keratinocytes) Anchored in a lipophilic matrix.[2]

Route of penetration

There are critically 3 ways in which a drug molecule will cross the intact SC: skin appendages (shunt routes),Through the intercellular lipid domains or by transcellular Route.[Figure: 2)

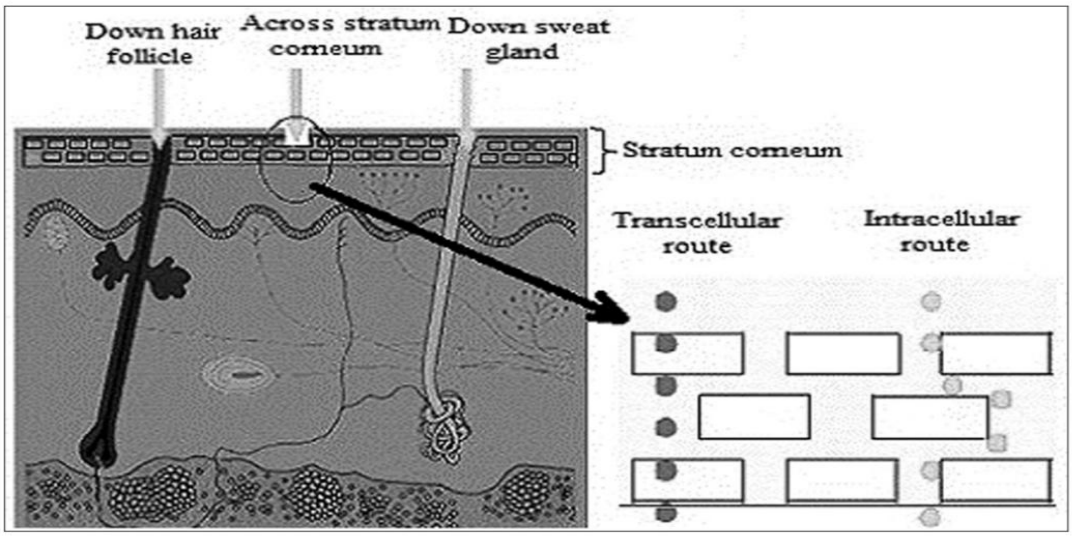


Figure 2 : penetration pathway across the skin [2]

The Appendageal route

The transappendageal routes are called the shunt Routes, and include permeation through the sweat glands and Across the hair follicles with their associated oily glands. Skin appendages give a continuous channel.Thetransappendageal routes are also known as the shunt Routes, and include permeation through the sweat glands and Across the hair follicles with their associated sebaceous glands. Skin appendages provide a continuous channel directly across the SC barrier.

Transcellular route

drugs entering the skin via the transcellular route pass through the corneocytes. Corneocytes containing extremely hydrated keratin provide an aqueous environment from which hydrophilic drugs will pass.

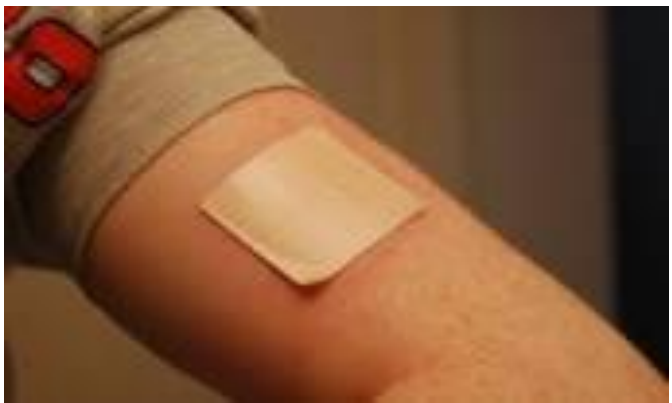
Intercellular route

The intercellular route involves drug diffusion through the continuous lipid matrix.This route is mostly accepted because the most common path for tiny uncharged molecules penetrating the skin.[2]

Transdermal patch

Definition

transdermal patch or skin patch patch that is placed on the skin to medication through the skin and



could be a medicated adhesive deliver a particular dose of into the bloodstream.[5]

Figure 3 : Transdermal Patch

Advantages Of Transdermal Patch

- Transdermal patches are painless.
- It is invasive thanks to deliver substances directly into body.
- Topical patches are a superior technique to deliver medications that aren't well absorbed from the mouth because of stomach acid breakdown significant liver degradation of the intestines.
- Topical patches applied to a steady, controlled the prolonged administration of drugs in time.
- There are fewer negative effects with topical patches.
- Topical patches are easier to apply.
- For people who cannot or do not wish to take drugs or supplements orally, topical patches offer an alternative.
- Topical patches are cheap.
- Topical patches are most popular by users.[5]
- Rejection of first pass metabolism.
- Rejection of gastro intestinal incompatibility
- predictable and prolonged length of activity.
- Provides utilization of pills with fast organic half Lives, slim therapeutic window.
- Enhance therapeutic efficacy.
- Drug administration stops with patch removal.[10]

Disadvantages of Transdermal Patch

- Only small, lipophilic tablets may be brought currently Through.
- Drug molecule must be potent because patch size Limits amount.
- Drugs with low or excess partition coefficient fail to reach blood circulation.
- Easy removal of drug transport in case of toxicity.
- Drugs which might be exceptionally melting may be given with the aid of using this Direction because of their low solubility each in water and fat.
- Erythema, itching, and edema may be caused by the drug, the adhesive, or different excipients with in the patch Formulation.[10]
- Transdermal drug shipping can’t deliver ionic capsules.
- Transdermal drug shipping device is restrained to effective drug.
- It can not deliver drug in a pulsatile design.
- Resilience actuating capsules or those (e.g., hormones) requiring chromo Pharmacological control isn’t suitable competitors.
- Required important lag time.
- Drug molecule having big atomic size (>a thousand Dalton) can not Produced for transdermal deliver.[6]

Types of Transdermal Patches

1. Single-layer Drug-in-Adhesive

The adhesive layer of this system additionally contains the drug. In this kind of patch the adhesive layer Now no longer best serves to stick the diverse layers Together, in conjunction with the complete device to the skin, However is likewise responsible for the releasing of the Drug. The adhesive layer is surrounded through a temporary liner and a backing.

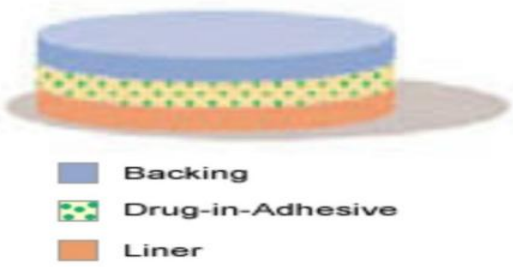


Figure 4 : Single -layer Drug -in- Adhesive

2. Multi-layer Drug-in-Adhesive

The multi-layer drug-in adhesive patch is similar to the single-layer machine in that each adhesive layers also are liable for the releasing of the drug. The multi-layer machine is special however that it provides some other layer of drug-in-adhesive, normally separated with the aid of using a membrane (however now no longer in all cases).This patch additionally has a temporary liner-layer and a everlasting backing.[5]

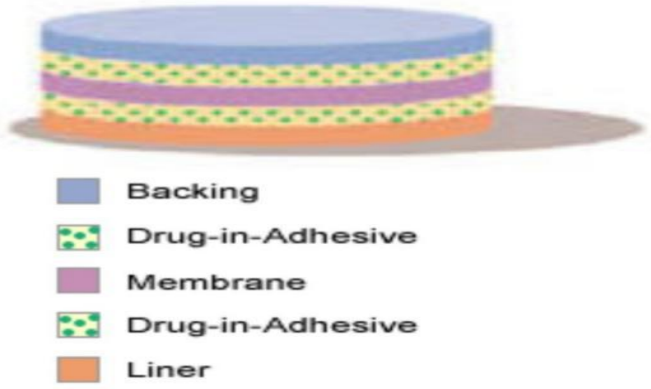


Figure 5 : Multi-layer Drug-in-Adhesive

3. Reservoir system

In this system the drug reservoir is embedded Among an impervious backing layer and a rate Controlling membrane. The drug releases only Through the rate controlling membrane, which may be Micro porous or non porous. In the drug reservoir Compartment, the drug may be in the shape of a Solution, suspension, gel or dispersed in a solid Polymer matrix. Hypoallergenic adhesive polymer May be implemented as outer surface polymeric membrane That's well suited with drug.[1]

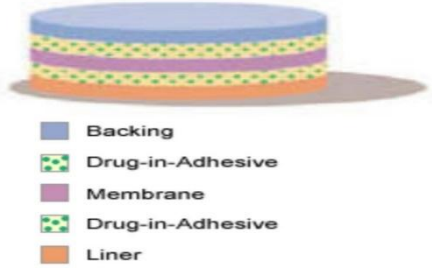


Figure 6 : Reservoir system

4. Matrix System

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer on this patch surrounds the drug layer in partially overlaying it.[5] Drug reservoir is prepared by dissolving the drug and polymer in a common solvent.[18]

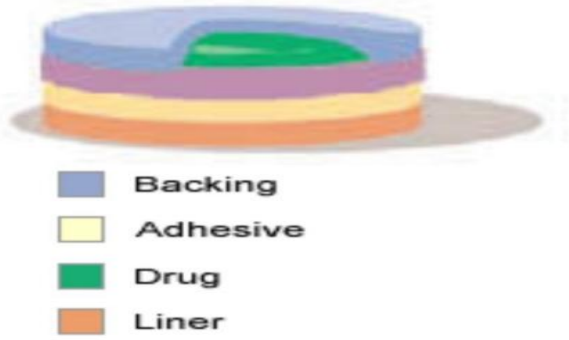


Figure 7 : Matrix s

5. Vapour Patch System

In this kind of patch the adhesive layer now no longer only Serves to stick the numerous layers collectively but Additionally to release vapour. The vapour patches are New available in the market and that they release important oils For up to six hours. The vapours patches launch Important oils and are utilized in case of Decongestion mainly. Other vapour patches on The market are controller vapour patches that Enhance the quality of sleep. Vapour patches that Reduce the amount of cigarettes that one smokes In a month also are available in the market.[5]

Basic Components of Transdermal Drug Delivery System

1. Polymer matrix/drug reservoir

Polymers are the backbone of TDDS, which manipulate the release of the drug from the system. A polymer matrix can be made by dispersion of drug in a liquid or solid state artificial polymer base. Polymers utilized in TDDS have biocompatibility and chemical compatibility with the drug and different additives of the system, together with penetration enhancers and PSAs. Additionally, they have to provide steady and powerful delivery of a drug all through the product's intended shelf-life, and have to be safe.

2. Membrane

A membrane can be sealed to the backing to shape a pocket to surround the drug-containing matrix or used as a single layer in the patch construction. The diffusion properties of the membrane are used to control availability of the drug and/or excipients to the skin. For example, ethylene vinyl acetate, silicone rubber, polyurethane, etc. are used as a rate-controlling membrane.

3. Drug

For successful developing TDDS, the drug ought to be Selected with great care. Transdermal patches provide many Benefits to drugs that go through extensive first-pass Metabolism, tablets with narrow therapeutic window or drugs With a short half-life, which cause noncompliance due to Common dosing.

Table 1 : Ideal properties of drugs for TDDS

Parameters	Properties
Dose	Should be low (less than 20 mg/day)
Half-life	10 or less (h)
Molecular weight	<400 Da
Partition coefficient	Log P (octanol–water) between 1.0 and 4.0
Skin permeability coefficient	$>0.5 \times 10^{-3}$ cm/h
Liophilicity	10 < Ko/w < 1000
Oral bioavailability	Low
Therapeutic index	Low
Melting point	<200°C
pH	Between 5.0 and –9.0

4. Permeation enhancers

One long-standing approach for enhancing TDD uses Penetration enhancers (additionally referred as sorption promoters or Accelerants), which increase the permeability of the SC so As to achieve better therapeutic levels of the drug candidate. Penetration enhancers interact with structural components Of the SC as consequence enhancing the barrier functions, leading to increased permeability. Three pathways are suggested For drug penetration through the skin: polar, nonpolar and polar/nonpolar.

5. Chemical enhancers

Chemicals that promote the penetration of topically applied Drugs are normally known as accelerants, absorption Promoters or penetration enhancers. Chemical enhancers Act by:

- Increasing (and optimizing) the thermodynamic activity Of the drug while functioning as a co-solvent.
- Increasing the partition coefficient of the drug to promote its release from the vehicle into the skin
- Conditioning the SC to promote drug diffusion.

6. Physical enhancers

Iontophoresis and ultrasound (additionally referred as phonophoresis or sonophoresis) strategies are examples of physical method of enhancement which have been used for enhancing Percutaneous penetration (and absorption) of various Therapeutic agents.

7. PSA

PSAs are the material that adhere to a substrate, on this case Skin, by application of mild pressure and leave no residue while Removed. They form interatomic and intermolecular attractive Forces on the interface, provided that the intimate contact is Formed. To achieve this degree of contact, the material must Be capable of deform below slight pressure, giving rise to the Term "pressure sensitive." Adhesion includes a liquid-like Flow, resulting in wetting of the skin floor upon the Application of pressure, and, while the pressure is removed, The adhesive units in that state. A PSA wets and spreads onto The skin while its surface energy is much less than that of the pores and skin. After the initial adhesion, the PSA/pores and skin bond may be built By stronger interactions (e.g., hydrogen bonding), which Will depend on pores and skin characteristics and other parameters. Widely used PSA polymers in TDDS are polyisobutylene-based Adhesives, acrylics and silicone-based PSAs, hydrocarbon Resin, etc. The PSA can be placed around the edge of the TDDS or be laminated as a non-stop adhesive layer on the TDDS surface.

8. Backing laminates

Backings are selected for appearance, flexibility and need For occlusion; hence, at the same time as designing a backing layer, the Consideration of chemical resistance of the material is most Important. Excipient compatibility must additionally be considered Because the extended contact between the backing layer And the excipients may also cause the additives to leach out of The backing layer or may also cause diffusion of excipients, Drug or penetration enhancer through the layer.

9. Release liner

During storage, the patch is covered by a protecting liner This is eliminated and discarded before the application of The patch to the skin. Because the lining is in intimate Contact with the TDDS, the lining must be chemically Inert.[2]

10. Penetration enhancers

Compounds which boost the entrance of topically Linked medicines are usually eluded as ingestion promoters, accelerants, or Penetration enhancers.

11. Sedate/prodrug

The prodrug technique has been applied to improve the dermal and transdermal conveyance of medicines with difficult phase Coefficients the prodrug configuration consists of expansion of a promoiety to build Segment coefficient and furthermore solvency and transport of the parent Tranquilize in the stratum corneum. Liposomes and vehicles-Liposome are colloidal particles shaped as concentric Bimolecular layers which are fit for epitomizing drugs. There are numerous cases of Restorative items wherein the dynamic fixings are epitomized in vesicles.

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Liposome are colloidal particles shaped as concentric bimolecular layers which are fit for epitomizing drugs. There are numerous cases of restorative items wherein the dynamic fixings are epitomized in vesicles.

13. Plasticizers

Plasticizers have likewise been utilized as a part of numerous Definitions going from 5 to 20% (w/w, dry premise). Ex: PEG 200, and PEG 400

14. Solvents

Various solvents, for example, methanol, chloroform,(CH3)2CO,Isopropanol and dichloromethane and so on are utilized to get ready medication store.[6]

Properties that influence transdermal drug Delivery

A. Biological Factors

(i). Skin Condition: Acids and alkalis, many Solvents like chloroform, methanol harm the skin Cells and promote penetration. Diseased state of Patient alters the skin conditions. The intact skin is Better barrier however the above mentioned conditions Have an effect on penetration.

(ii). Skin age: The young skin is more permeable than older. Children are more sensitive for skin absorption of toxins. Thus, skin age is one in all the factor affecting penetration of drug in TDDS.

(iii). Blood supply: Changes in peripheral circulation can have an effect on transdermal absorption.

(iv). Regional skin site: Thickness of skin, nature of stratum corneum and density of appendages changes site to site. These elements have an effect on significantly penetration.

(v). Skin metabolism: Skin metabolizes steroids, hormones, chemical cancer agents and a few drugs. So skin metabolism determines efficacy of drug permeated through the skin.

(vi). Species differences: The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration.

B. Physicochemical factors

(i). Skin hydration: In contact with water the permeability of skin will increase significantly. Hydration is maximum critical aspect increasing the Permeation of skin. So use of humectant is done in Transdermal delivery.

(ii). Temperature and pH: The permeation of drug increase ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on The pH and pKa or pKb values. The proportion of Unionized drug determines the drug concentration In skin. Thus, temperature and pH are important Factors affecting drug penetration.

(iii). Diffusion coefficient: Penetration of drug depends on diffusion coefficient of drug. At a steady temperature the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction among them.

(iv). Drug concentration: The flux is proportional to the concentration gradient throughout the barrier and concentration gradient can be better if the concentration of drug can be greater across the barrier.

(v). Partition coefficient: The optimal partition coefficient (K) is needed for appropriate action. Drugs with excessive K aren't ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.

(vi). Molecular size and shape: Drug absorption is inversely associated with molecular weight, small molecules penetrate faster than large ones.[1]

C. Environmental factors

(i). Sunlight : Because of to sunlight, the walls of blood vessels become Thinner, leading to bruising, with only minor trauma in the Sun-exposed areas. Also, pigmentation, the most noticeable Sun-induced pigment change, is a freckle or solar lentigo.

(ii). Cold season : The cold season often results in itchy and dry skin. The skin Responds by increasing oil production to compensate for the Weather's drying effects. A good moisturizer will help ease Symptoms of dry skin. Also, drinking lots of water can keep Your skin hydrated and looking radiant.

(iii). Air pollution : Dust can clog pores and increase bacteria on the face and the Surface of skin, both of which lead to acne or spots, which Affects drug delivery through the skin. Invisible chemical Pollutants in the air can interfere with the skin's natural Protection system, breaking down the skin's natural oils That normally trap moisture in the skin and keep it supple.[2]

General clinical considerations in the use of TDDS

The patient should be informed of the following general guidelines. The patient should be informed of the importance of using the recommended site and rotating sites within the site. The pivot point is important to allow the skin to regain its normal permeability and prevent skin irritation.

1. TDDS should be applied to clean, dry skin that is relatively hair-free and not oily, inflamed, irritated, or cracked. Wet or damp skin can speed up drug penetration.Oily skin may affect the adhesion of the patch. If there is hair at the site, it should be carefully trimmed, not wet shaved or a depilatory used, as this can remove the stratum corneum and affect the speed and extent of drug permeation.
2. The use of skin lotions at the application site should be avoided as lotions may affect skin hydration and alter the partition coefficient of the drug.
3. The patient must not physically tamper with the TDDS as this will destroy the integrity of the system. pull out carefully so as not to touch your fingertips.
4. The TDDS should be pressed firmly against the skin site with the palm of your hand for approximately 10 seconds.
5. The TDDS should be placed in a location that will not be subject to friction from clothing or movement. The TDDS must remain on while showering, bathing or swimming.
6. A TDDS should be worn for the period specified in the product instructions after it has been removed and replaced with a new system.
7. The patient or caregiver should wash their hands after applying a TDDS the patient should not rub their eyes or touch their mouth while handling the system. If the patient demonstrates sensitivity or intolerance to a TDDS or if excessive skin irritation occurs, the patient should seek further evaluation.
8. When removing, a used TDDS should be folded. in half with adhesive layer attached so it cannot be reused. The used patch is disposed of safely for children and pets.[1]

Popular Use

- The best-selling transdermal patch in the United States is the nicotine patch, which releases nicotine in controlled doses to help quit smoking. The first commercially available vapor patch to reduce smoking was approved in Europe in 2007.
- Two opioid drugs used to relieve severe pain around the clock are commonly prescribed in patch form: fentanyl (marketed as Duragesic) and buprenorphine (marketed as BuTrans).
- Estrogen patches are also sometimes prescribed to treat menopausal symptoms. such as postmenopausal osteoporosis.
- Other transdermal patches for hormone delivery include the contraceptive patch (marketed as Ortho Evra or Evra).
- Nitroglycerin patches are sometimes prescribed to treat angina instead of sublingual pills.
- The blood pressure-lowering drug clonidine is available in a transdermal patch form under the Brand names Catapres-TTS.
- Emsam, a transdermal form of the MAOI selegiline, was approved in the US in March 2006 as the first transdermal delivery vehicle for an antidepressant.[5]

Adverse Effects

In 2005, the FDA announced that it was investigating reports of deaths and other serious adverse events associated with narcotic overdoses in patients using Duragesic, the fentanyl transdermal patch used to control pain. Duragesic's product label was later updated in June 2005 to add safety information to its Versions of the patch due to a manufacturing defect that allowed the gel containing the drug to leak out of the sachet too quickly, potentially leading to an overdose and death. As of 2010, Sandoz no longer uses gel in its fentanyl transdermal patch; Instead, Sandoz brand fentanyl patches use an adhesive matrix/suspension (where the drug is mixed with the adhesive rather than being stored in a separate pouch with a porous membrane), similar to other fentanyl patch manufacturers such as Mylan and Jansen. Metal-containing transdermal patches have been associated with skin burns at the time of shock therapy with external and internal cardioverter defibrillators (ICDs) [5]

Conditions in which transdermal patches are used

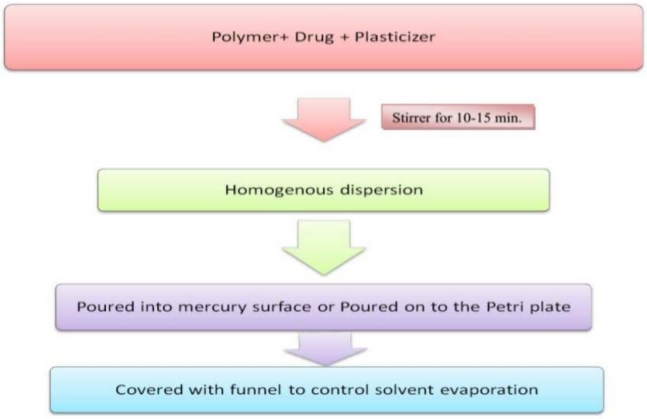
1. When the patient has intolerable side effects (including constipation) and does not are able to take oral medication (dysphagia) and want an alternative method of drug delivery where pain control could be improved through reliable delivery.
2. This could be useful for patients with cognitive impairment or those unable to self-medicate with their pain medication.
3. It can be used in combination with other enhancement strategies to achieve synergistic effects.[8]

Conditions where transdermal patches are not used

1. Treatment of acute pain is required.
2. When rapid dose titration is required.
3. When the required dose is 30 mg/24 hours or less.[8]

Method of manufacturing the transdermal patch

The method of manufacturing TDDS has been summarized by modifying the previously reported methods.



The patches were made using the solvent casting process. The polymer (e.g. PVP/HPMC) was taken up in a beaker with a minimal amount of solvent. Then 2/3 of the solvent was mixed with the other polymers (e.g. PVA) and added first with stirring at lower speed and then at higher speed. The emollient was added and mixed homogeneously and the drug incorporated with continued agitation and volume completed. Films were placed in a suitably designed and fabricated glass mold and then dried in an oven at 40°C. The films were removed with a sharp blade inserted along the edges of the film. The dried films were wrapped in parchment paper. And kept in a closed container away from light and in a cool place.[14]

Take care when applying the transdermal patch

The skin part should be thoroughly cleaned before applying the patch. Cutting the patch will destroy the drug delivery system, so the patch should not be cut. You should make sure to remove the old patch from the website before applying a new one. Patch. Care should be taken when applying or removing the patch as anyone handling the patch can absorb it.The patch should be applied accurately to the site of administration.[1]

Figure 8 : Instructions for Applying Transdermal Patch

It is important to use a different application site Everyday to avoid skin irritation. Suggested rotation is :

Day 1 – Upper right arm Day 2 – upper right chest

Day 3 – Upper left chest. Day 4 – Upper left arm, Then repeat from Day 1[1]

Mechanism of action of Transdermal Patch

Application of the transdermal patch and the Flow of the active drug constituent from the patch. To the circulatory system via skin occur through Various methods.

1. Iontophoresis : It passes a few milliamperes of Current to a few square centimeters of skin Through the electrode placed in contact with the Formulation, which facilitates drug delivery Across the barrier. Mainly used of pilocarpine Delivery to induce sweating as part of cystic Fibrosis diagnostic test. Iontophoretic delivery of Lidocaine appears to be a promising approach for Rapid onset of anesthesia.

Figure 9 : Iontophoresis

2. Electroporation : It is a method of application of short, high-voltage electrical Pulses to the skin. After electroporation, the permeability of the skin for diffusion of drugs is increased by 4 orders of magnitude. The electrical pulses are believed to form transient aqueous pores in the stratum corneum, through which drug transport occurs. It is safe and the electrical pulses can be administered painlessly using closely spaced electrodes to constrain the electric field within the nerve-free stratum corneum.

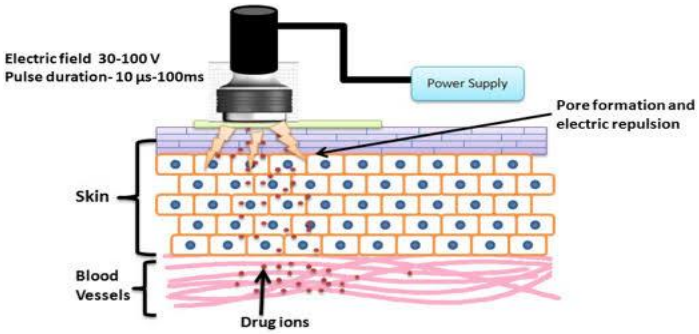


Figure 10 : Electroporation

3. Application by ultrasound : Application of ultrasound, particularly low frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules. It is also known as sonophoresis. Katz et al. reported on the use of low-frequency sonophoresis for topical delivery of EMLA cream.

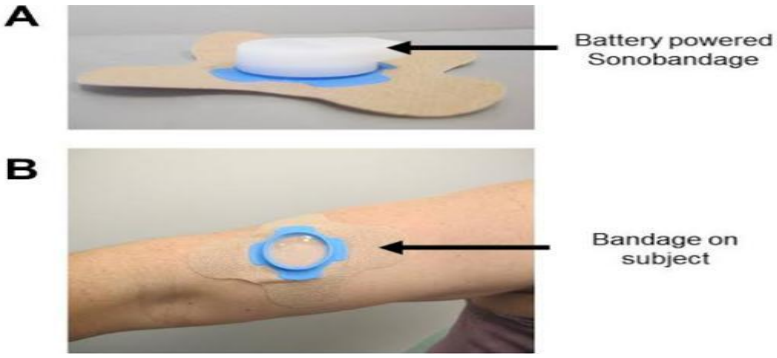


Figure 11 : Ultrasound

4. Use of microscopic projection : Transdermal patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. Needles ranging from approximately 10-100 µm in length are arranged in arrays. When pressed into the skin, the arrays make microscopic punctures that are large

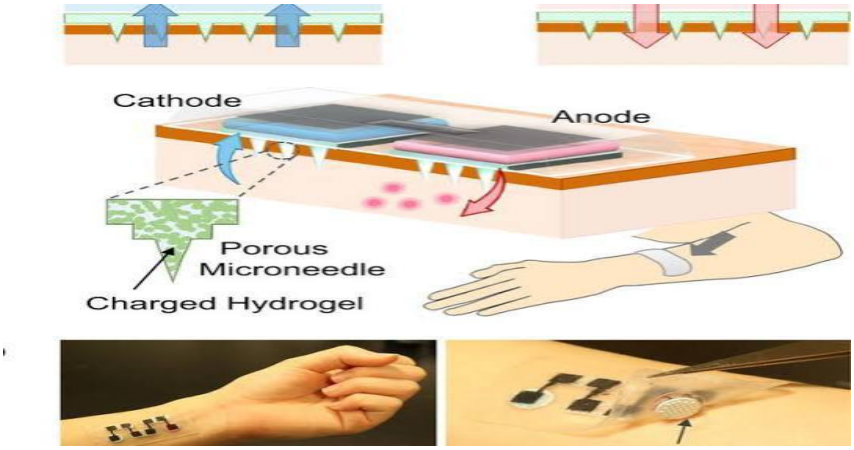


Figure 12 : Microneedle

enough to deliver macromolecules, but small enough that the patient does not feel penetration or pain. The drug is coated on the surface of the microneedles to aid in rapid absorption. They are used in the development of skin vaccines against tetanus and influenza. Several other methods are also used for transdermal patch application such as: B. thermal poration, magnetophoresis, and photomechanical waves.[5]

Evaluation of transdermal patches

A. Physicochemical Evaluation

1.Thickness: The thickness of the transdermal film is determined using a portable microscope, a dial gauge, a micrometer or a micrometer at very different points on the film.

2. Weight Uniformity: Weight variation is examined by weighing 10 randomly selected spots separately and calculating the average weight. The individual weight should not deviate significantly from the average weight.

3. Drug content Determination: precisely weighed portion of the film (approx. 100 mg) is dissolved in 100 ml of a suitable solvent in which the active substance is soluble and the solution is then stirred continuously for 24 h in a shaking incubator. Then the total solution, after sonication and subsequent filtration, the active ingredient in solution is estimated spectrophotometrically by appropriate dilution.

4. Content Uniformity Test: 10 patches are selected and the content for individual patches is determined. the declared value and a content of not less than 75% to 125% of the declared value, the transdermal patches pass the content uniformity test. However, if 3 patches fall within the range of 75% to 125%, an additional 20 patches are tested for potency.

To pass the test Transdermal patch must have content uniformity of 75% to 125%

5. Moisture content: Prepared films are weighed separately and stored in a desiccator containing calcium chloride for 24 hours at room temperature. The films are weighed again after a set interval until they have a constant weight.

% moisture content = initial weight - final weight × 100

6. Moisture absorption: The heavy films are kept in a desiccator at room temperature for 24 h. They are then removed and exposed to 84% relative humidity using saturated potassium chloride solution in a desiccator until constant weight is reached

% Moisture Uptake = Final Weight - Initial Weight × 100

7. Flatness: A transdermal patch should have a smooth surface and not shrink over time currently. This can be proven with a flatness study.To determine flatness, cut one strip from the center and two from each side of the patches. The length of each strip and the change in length are measured to determine the percent constriction. Zero percent necking corresponds to 100% flatness.

% Constriction = I1 - I2 X 100

I2 = final length of each strip ,I1 = initial length of each strip

8. Folding Endurance: Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value.

9. Tensile Strength: To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted.

Tensile Strength= F/a.b (1+L/1)

F is the force required to break; **a** is width of film; **B** is thickness of film; **L** is length of film; **l** is Elongation of film at break point.

10. Tack properties: It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer.

11. Thumb tack test: The force required to remove thumb from adhesive is a measure of tack.

12. Rolling ball test: This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.

13. Quick stick (Peel tack) test: The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90 at the speed of 12 inch/min.

14. Probe tack test: Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.

B. Invitro release study

1. The Paddle over Disc: (USP apparatus 5/ PhEur 2.9.4.1) This technique is just like the USP Paddle dissolution apparatus, except that the Transdermal system is connected to a disc or cell Resting at the bottom of the vessel that contains Medium at thirty two ±5°C.

2. The Cylinder modified USP Basket: (USP Apparatus 6 / PhEur 2.9.4.3) This method is Similar to the USP basket sort dissolution Apparatus, except that the system is attached to The surface of a hollow cylinder immersed in Medium at thirty two ±5°C.

3. The reciprocating disc: (USP equipment 7) In this technique patches connected to holders are oscillated in tiny volumes of medium, permitting the apparatus to be helpful for systems delivering Low concentration of drug.[5]

C. Invivo study

1. Animal models : For in-vivo studies animals are generally preferred at small scale because of easily availability and economically view. In human, considerable time and resources are required for study. The animal species used in in-vivo study are: rat guinea pig, hairless mouse, hairless rat, hairless dog, cat horse, goat, rhesus monkey, miniature pig, squirrel, chimpanzee, etc. The most preferred animal used in in-vivo study is rhesus monkey.

2. Human volunteers: The ultimate stage during clinical phases in development of transdermal devices is collection of all pharmacokinetic and pharmacodynamic data from human volunteers which were required to evaluate any toxic effects generate during application of formulations.[7]

Examples of marketed transdermal drug delivery Systems [1]

Therapeutic agent	**TDDS**	**Design**
Clonidine	Catapres-TTS (Boehringer Ingelheim	Four layer patch
Estradiol	Estraderm(Novartis)	Four layer patch
Estradiol	Vivelle(Novartis)	Three layer system
Estradiol	Climara (Novartis)	Three layer system
Fentanyl	Duragesic (Janssen)	Four layer system
Nicotine	Prosstep (Lederie)	Multistep round patch
Testosterone	Testoderm (Alza)	Three layer patch
Nicotine	Habitrol (Novartis Consumer)	Multilayer round patch
Nicotine	Nicoderm CQ (Smithkline Beecham Consumer)	Multilayer rectangular patch
Nicotine	Nicotrol (McNell Consumer)	Multilayer rectangular patch

Recent advances in transdermal Delivery system :

Latest research done in field of transdermal patches

1. Patch technology for protein delivery:-Transdermal delivery of large protein is a novel and exciting delivery method trans pharma uses its unique printed patch technology for transdermal delivery of protein thereby complementing its via Derm delivery technology. It is postulated that the highly water soluble proteins are dissolved by the interstitial fluid that is secreted from the skin through the RF- MicroChannels, forming a highly concentrated protein solution in situ.The delivery of the dissolved molecules is then carried out, via the RF- Micro Channels, into the viable tissues of the skin, diffusing across a steep concentration gradient.

2. Testosterone transdermal patch system in young women with spontaneous premature ovarian failure:-In premenopausal women, the daily testoterone production is approximately 300 µg, of which approximately half is derived from the ovaries and half from the adrenal glands. Young women with spontaneous premature ovarian failure (sPOF) may have lower androgen levels, compared with normal ovulatory women. Testosterone transdermal patch (TTP) was designed to deliver the normal ovarian production rate of testosterone.

3. Transdermal patch of oxybutynin used in overactive bladder:- The product is a transdermal patch containing Oxybutynin HCl and is approved in US under the brand name of Oxytrol and in Europe underthe brand name of Kentera. OXYTROL is a thin, flexible and clear patch that is applied to the abdomen, hip or buttock twice weekly and provides continuous and consistent delivery of oxybutynin over a three to four day interval.

4. Nanotechnology gaining hold:-This technology combines the advantage of a needle and the transdermal patch. The devices are dime- sized pieces of polymer with hundreds of hollow microneedles between 100 and 1,000 micrometers long.These small needles penetrate the top layers of skin and allow the drug to pass through with ease.

5. Pain relief:-Pain relief routinely benefits from transdermal patch technology. Most of the readers are aware of the Duragesic patch. One is Lidoderm, a lidocaine percent patch, which is used for post herpetic neuralgia. Other exciting advancements in pain control include the E- Trans fentanyl HCl patch.This credit card- size patch is an active delivery device that has a self- contained battery that delivers pulses of fentanyl HCl, a strong narcotic. This mimics the use of intravenous self- controlled analgesic systems that are very expensive.

6. Poke with patch approach:-Involves piercing into the skin followed by application of the drug patch at the site of treatment.

7. Coat and poke approach:-Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.

8. Biodegradable micro needles:- Involves encapsulation of the drug within the biodegradable.[12]

Future Technologies And Approaches

1) Jet injectors are receiving increased attention now days, that is opening doors for improved device design for controlled, needle free injection of drug solutions across the skin and into deeper tissue.
2) Tiny needle is inserted a few millimeters into skin and Drug solution is flowed through the needle into the skin At controlled rates using a micro- infusion pump that is Contained among a large patch affixed to skin, Morphine has been delivered to humans using this approach.
3) During the past decade many theories are put Forward in addressing the combinations of chemicals And iontophoresis; chemicals and electroporation; Chemicals and ultrasound; iontophoresis and Ultrasound; electroporation and iontophoresis; and Electroporation and ultrasound.
4) TransPharma is focused on products for which our technology can give clear benefits over existing therapies. Such benefits may include improving safety and compliance through the use of a drug patch or enhancing efficacy with the use of sustained release patch formulations, among others.
5) The ViaDerm system might be applied to the delivery of local medications for topical applications within the fields Of dermatology and cosmetics. The ViaDerm system May also allowenhancedimmunisations, providing a Nonpainful, safe and effective different to current Intramuscular or subcutaneous vaccination methods.[10]
6) Modifications are largely restricted to refinements of the materials used.[14]
7) Different potential enhancements include improved transdermal technology that utilizes mechanical energy to increase drug flux across the skin either by altering the skin barrier or increasing the energy of the drug molecules. After the successful design of patches using iontophoresis, numerous modes of 'active' transdermal technologies are being investigated for totally different drugs. These include electroporation (short electrical pulses of high voltage to make transient aqueous pores within the skin), sonophoresis (uses low frequency skin), sonophoresis (uses low frequency ultrasonic energy to Disrupt the stratum corneum), and thermal energy (uses heat To make the skin more permeable and to extend the energy of Drug molecules).[22]

Conclusion

Basic functions of the skin are protection and Containment, it might seem exceptionally difficult To target the skin for drug delivery. However,with Our greater understanding of the structure and Function of the skin, and how to change these Properties, more and more new drug products are Being developed for transdermal delivery. The foregoing shows that TDDS have great potentials, being Able to use for each hydrophobic and hydrophilic active Substance into promising deliverable drugs After preparation Of transdermal patches, consistent methodologies are Adopted to check the various parameters. In the present time due to certain disadvantages like large Drug molecules cannot be delivered, large dose cannot be given, the Rate of absorption of the drug is less, skin irritation, and etc. the use Of the Transdermal Drug Delivery System has been limited. Drug molecules may be redesigned To achieve higher skin penetration. Most drugs in the Market nowadays were not only structured to elicit a particular pharmacological response, but also designed to Have appropriate solubilities, particularly with respect To oral and parenteral dosage forms. Transdermal dosage forms may offer Clinicians an opportunity to supply more therapeutic options to Their patients to optimize their care. TDDS used for the used for drug therapy for a Less absorption, more uniform plasma levels, improved Bioavailability, decrease aspect effect, efficacy and quality of The product. In recent years, the dimensions of TDDS within the domestic and Overseas drug delivery system market has increased, as Confirmed through increasing analysis studies, patents, and commercially offered products from several firms and research institutes. This provides valuable info Relating to the formulation and evaluation aspects of Transdermal drug delivery systems as a ready reference for The research scientists who are involved in TDDS.

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