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TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

A transdermal patch may be a medicated adhesive patch that is placed on the skin to deliver a particular dose of medication through the skin and into the blood. Often, this promotes healing to injured space of the body. A bonus of a transdermal drug delivery route over different sorts of medication delivery like oral, topical, blood vessel, contractor, etc. is that the patch provides a controlled release of the medication into the patient, sometimes through either a porous membrane covering a reservoir of medication or through body heat melting skinny layers of medication embedded within the adhesive. The most disadvantage to transdermal delivery systems stems from the actual fact that the skin may be a very effective barrier; as a result, solely medications whose molecules are sufficiently little to penetrate the skin will be delivered during this technique. A good selection of prescribed drugs are currently on the market in transdermal patch form.

INTRODUCTION

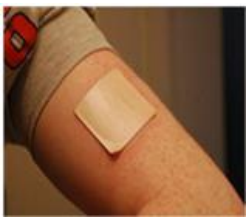
Transdermal patch (Skin patch) uses a special membrane to regulate the speed at which the liquid drug contained within the reservoir within the patch will undergo the skin and into the blood. Some medication should be combined with substances, like alcohol, that increase their ability to penetrate the skin so as to be employedin a transdermal patch. Medication administered through skin patches embody hyoscine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to forestall osteoporosis when menopause), nitroglycerin (f or angina), and local anesthetic to alleviate the pain of shingles (herpes zoster). Molecules of insulin and many different substances, however, are large to go through the skin. Patches applied to the skin eliminate the requirement for vascular access by syringe or the utilization of pumps.

Transdermal patches were developed in the 1970s and also 1st was approved by the FDA in 1979 for the treatment of motion sickness. It had been a three-day patch that delivered scopolamine. In 1981, patches for trinitroglycerin were approved, and nowadays there exist variety of patches for medication like Catapres, fentanyl, lidocaine, nicotine, trinitroglycerin, oestradiol, oxybutinin, scoplamine, and testosterone. There are combination patches for contraception, likewise as endocrine replaceme nt. Depending on the drug, the patches typically last from one to seven days. The major advantages provided by transdermal drug delivery embrace the following: improved bioavailability, more uniform plasma levels, longer period of action leading to reduction in dosing frequency, reduced aspect effects and improved medical aid due to maintenance of plasma levels up to the tip of the dosing interval compared to a decline in plasma levels

with conventional oral dosage forms. Transdermal patches are helpful in developing new applications for existing medical specialty and for reducing first-pass drug-degradation effects. Patches also can cut back aspect effects; for example, estradiol patches are employed by more than a million patients annually and, in contrast to oral formulations, do not cause liver damage. Of 2 major sub-categories – (therapeutic and cosmetic), aroma patches, weight loss patches, and Non-medicated patch markets embrace thermal and cold patches, nutrient patches, skin care patches (a class that consists patches that measure daylight exposure).

Definition

A transdermal patch or skin patch 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.



Advantages of transdermal patches

The advantages of transdermal delivery are obvious even delivery of a therapeutic level of drug is painless, the patient does not need to inject himself, there are no bulky delivery devices to manage or dangerous needles to eliminate, and there are few or no duct effects from the drug itself. Peak plasma levels of the drug are reduced, Resulting in remittent aspect effects. Additionally, transdermal delivery is helpful for those drugs that have a high first pass result through the liver, have poor oral uptake, need frequent administration, or that act with stomach acid. The first pass result ends up in the destruction of a major quantity of the drug. Drugs absorbed through the skin, however, enter the general circulation directly avoiding the liver, with less total drug absorption occurring

Topical patches are a painless, non-invasive way to deliver substances directly into the body.

Topical patches are a much better way to deliver substances that are brokendown by the stomach acids, not well-absorbed from the gut, or extensively degraded by the liver.

Topical patches over a controlled, steady delivery of medication over long periods of time. Topical patches have fewer aspect effects than oral medications or supplements. Topical patches are easier to use and remember. Topical patches over an alternative to people who cannot, or prefer not to take medications or supplements orally. Topical patches are efficient. People prefer topical patches. Limitations of Transdermal drug delivery system:

TDDS cannot deliver ionic medication.

TDDS cannot attain high drug levels in blood/plasma.

It cannot develop for medication of large molecular size.

TDDS cannot deliver medication in a pulsatile fashion.

TDDS cannot develop if drug or formulation causes irritation to skin.

Limitation of TDDS can be overcome to some extent by novel approaches such as Iontophoresis, electroporation and ultrasound.

Popular uses

The very best selling skin patch in the United States is that the phytotoxin patch, which releases phytotoxin in controlled doses to assist with stop of tobacco smoking. The first commercially obtainable vapour patch to scale back smoking was approved in Europe in 2007.Two opioid medications accustomed offer round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans). Estrogen patches are generally prescribed to treat biological time symptoms as well as post-menopausal osteoporosis. Other transdermal patches for internal secretion delivery embody the contraceptive patch (marketed as Ortho Evra or Evra). Vasodilative patches are generally prescribed for the treatment of angina in lieu of articulator pills. The anti-hypertensive drug Clonidine is available in skin patch type under the name Catapres-TTS. 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.

Adverse events

In 2005, the FDA declared that they were investigating reports of death and different serious adverse events associated with narcotic overdose inpatients victimization Duragesic, the Sublimaze transdermic patch for pain management. The Duragesic product label was afterwards updated to feature safety information in June 2005. 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 because of a producing defect that allowed the gel containing the medication to leak out of its pouch too quickly, that may end in overdose and death. As of 2010, Sandoz no longer uses gel in its transdermal fentanyl patch; instead, Sandoz-branded fentanyl patches use a matrix/adhesive suspension (where the medication is mixed with the adhesive instead of command in an exceedingly separate pouch with a porous membrane), kind of like alternative fentanyl patch manufacturers like Mylan and Janssen. In 2007, Shire and Noven Pharmaceuticals, manufacturers of the Daytrana ADHD patch,
announced a voluntary recall of several lots of the patch because of issues with separating the patch from its protective release liner. Since then, no further issues with either the patch or its protective packaging are reportable. In 2009, the FDA proclaimed a public health advisory warning of the danger of burns throughout MRI scans from transdermal drug patches with metallic backings. Patients ought to be suggested to remove any medicated patch before an MRI scan and replace it with a brand new patch when the scan is complete. Skin burns have occurred with metal containing transdermal patches at the time of shock treatment from external further as internal cardioverter defibrillators (ICD). The main components to a transdermal patch are:

- ✓ Liner - Protects the patch during storage. The liner is removed prior to use.
- ✓ Drug - Drug solution in direct contact with release liner.
- ✓ Adhesive - Serves to adhere the components of the patch together along with adhering the patch to the skin.
- ✓ Membrane - Controls the release of the drug from the reservoir and multi-layer patches.
- ✓ Backing - Protects the patch from the outer environment

Conditions in which Transdermal patches are used:Transdermal patch is employed when: (1)When the patient has intolerable aspect effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternate technique of drugdelivery.
(2) Wherever the pain management may well be improved by reliable administration. This might be useful in patients with psychological feature impairment or people who for alternative reasons are not able to self-medicate with their physiological condition.
(3) It may be employed in combination with alternative enhancement methods to produce synergistic effects.

Conditions in which transdermal patches are not used:

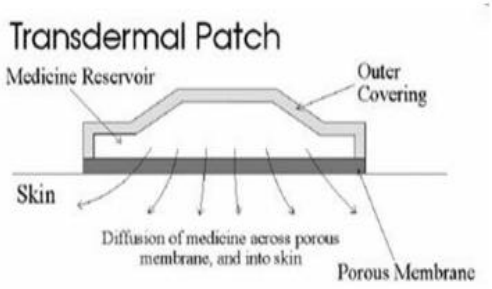
The use of patch is not appropriate when:
(1)Cure for acute pain is needed.
(2) Wherever fast dose volumetric analysis is needed.
(3) Wherever demand of dose is equal to or less than 30 mg/24hrs.

Factors affecting transdermal bioavailability- Two major factors have an affect on the bioavailability of the drug via transdermal routes:
(1)Physiological factors
(2)Formulation factors

Physiological factors embody

(1)Stratum corneum layer of the skin
(2)Anatomic website of application on the body
(3) Skin condition and disease

(4) Age of the patient
(5)Skin metabolism
(6) shedding (peeling or flaking of the surface of the skin)
(7) Skin irritation



Formulation factors embody

(1)Physical chemistry of transport
(2) Vehicles and membrane used
(3) Penetration enhancers used
(4) Methodology of application
(5) Device used

Care taken while applying skin patch

(1)The part of the skin wherever the patch is to be applied ought to be properly clean.
(2) Patch should not be cut as a result of cutting the patch destroys the drug delivery system.
(3) Before applying a replacement patch it should be made sure that the previous patch is removed from the positioning.
(4) The patch should be applied accurately to the site of administration.

Mechanism of Action of Transdermal Patch: The application of the skin patch and also the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods.

1. Iontophoresis- Iontophoresis passes some milliamperes of current to some square centimeters of skin through the conductor placed involved with the formulation, that facilitates drug delivery across the barrier. Principally used of alkaloid delivery to induce sweating as a part of cystic fibrosis assay. Iontophoretic delivery of lidocaine seems to be a promising approach for rapid onset of anesthesia.

2.Electroporation- Electroporation could be a technique of application of short, high-voltage electrical pulses to the skin. After electroporation, the porosity of the skin for diffusion of drugs is enhanced by four orders of magnitude. The electrical pulses are believed to form transient binary compound pores within the stratum corneum, through that drug transport happens. It is safe and also the electrical pulses can be administered painlessly using closely spaced electrodes to constrain the electrical field among the nerve-free stratum.

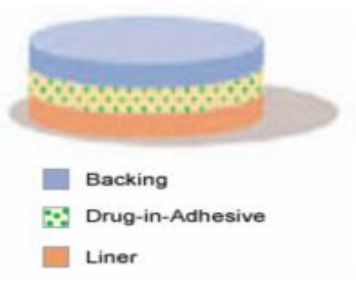
3. Application by ultrasound- Application of ultrasound, notably low frequency ultrasound, has been shown to reinforce transdermal transport of varied medication as well as macromolecules. It is additionally referred to as sonophoresis. Katz et al. reported on the employment of low-frequency sonophoresis for topical delivery of EMLA cream.

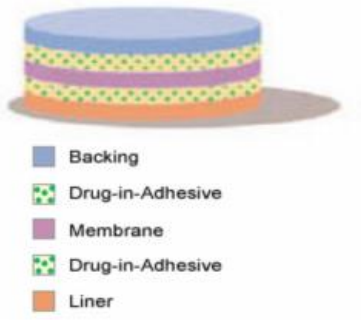
4. Use of microscopic projection- Transdermal patches with microscopic projections referred to as microneedles were used to facilitate stratum drug transport. Needles ranging from more or less 10-100 µm long are organized in arrays. Once pressed into the skin, the arrays create microscopic punctures that are giant enough to deliver macromolecules, but small enough that the patient does not feel the penetration or pain. The drug is surface coated on the microneedles to assist in speedy absorption. They are utilized in development of cutaneous vaccines for tetanus and influenza. Various different ways are used for the application of the stratum patches like thermal poration, magnetophoresis, and photomechanical waves. However, these ways are in their early stage of development and required additional detail finding out.

Types of Transdermal Patch

Single-layer Drug-in-Adhesive- The adhesive layer of this technique additionally contains the drug. In this kind of patch the adhesive layer not solely serves to stick the varied layers together, at the side of the complete system to the skin, but is additionally chargeable for the release of the drug. The adhesive layer is encircled by a temporary liner and a backing.

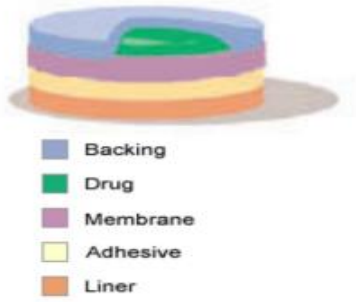
Multi-layer Drug-in-Adhesive- The multi-layer drug-in adhesive patch is analogous to the single-layer system in that each adhesive layers are chargeable for the releasing of the drug. The multi-layer system is completely different but that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch additionally contains a temporary liner-layer and a permanent backing.





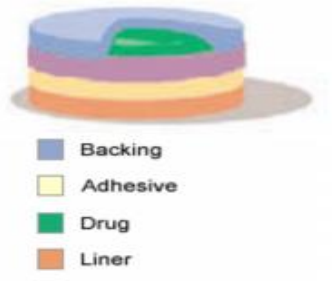
Reservoir

Unlike the Single-layer and Multi-layer Drug-in-adhesive systems the reservoir transdermal system contains a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is additionally backed by the backing layer. In this type of system the rate of release is zero order.



Matrix

The Matrix system incorporates a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer during this patch surrounds the drug layer partially overlaying it.



Brand Name	Drug	Manufacturer	Indications
Nicotinell®	Nicotine	Novartis	Pharmacological smoking cessation
Matrifen®	Fentanyl	Nycomed	Pain relief patch
Ortho Evra™	Norelgostromin/ Ethinyl Estradiol	ORTHO-McNEIL	Postmenstrual syndrome
NuPatch 100	Diclofenac diethylamine	Zydus Cadila	Anti-Inflammatory
Neupro®	Rigotine	UCB and Schwarz Pharma	early-stage idiopathic Parkinson's disease
Alora	Estradiol	TheraTech/Proctol and Gamble	Postmenstrual syndrome
Nicoderm®	Nicotine	Alza/GlaxoSmithKline	Smoking cessation

Vapour Patch

In this variety of patch the adhesive layer not solely serves to stick the assorted layers together however also to unleash vapour. The vapour patches are new on the market and that they unleash essential oils for up to six hours. The vapours patches unleash essential oils and are employed in cases of decongestion chiefly. Different vapour patches on the market are controller vapour patches that improve the standard of sleep. Vapour patches that reduce the number of cigarettes that one smokes in a month are out there on the market.

Evaluation of transdermal patches

Physicochemical evaluation

- ✓ In vitro evaluation
- ✓ In vivo evaluation

Physicochemical Evaluation:

Thickness: The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at completely different points of the film.

Uniformity of weight: Weight variation is studied by one by one consideration ten randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination: An accurately weighed portion of film (about 100 mg) is dissolved in 100 ml of appropriate solvent

during which drug is soluble so the solution is jolted continuously for 24 h in shaker incubator. Then the whole solution is sonicated. when sonication and resultant filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

Content uniformity test: Ten patches are selected and content is set for individual patches. If 9 out of 10 patches have content between 85% to 115% of the desired value and one has content not less than 75% to a hundred and 125% of the specified value, then transdermal patches pass the test of content uniformity. However if 3 patches have content within the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

Moisture content: The ready films are weighed one by one and kept in desiccators containing salt at temperature for 24 h. The films are weighed again after a specified interval till they show a relentless weight. The % moisture content is calculated using following formula.

% Moisture content = Initial weight – Final weight X 100

Moisture Uptake: Weighed films are kept in a desiccator at room temperature for 24h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator till a relentless weight is achieved. % moisture uptake is calculated as given below.

% moisture uptake = Final weight – Initial weight X 100

Flatness: A skin patch ought to possess a smooth surface and should not constrict with time. This could be incontestable with flatness study. For flatness determination, one strip is cut from the centre and two from both sides of patches. The length of every strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100% flatness.

% constriction = I1 – I2 X 100

I2 = Final length of each strip

I1 = Initial length of each strip

Folding Endurance: Analysis 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 till it break. The amount of times the films might be folded at an equivalent place without breaking is folding endurance value.

Tensile Strength: To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One finish of the films is kept mounted with the assistance of an iron screen and other finish is connected to a freely movable thread over a pulley. The weights are added bit by bit to the pan hooked up with the hanging finish of the thread. A pointer on the thread is employed to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation.

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

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.

Tack properties: It is the power of the polymer to adhere to substrate with very little contact pressure. Tack relies on mass and composition of polymer yet as on the utilization of tackifying resins in polymer.

Thumb tack test: The force needed to get rid of thumb from adhesive could be a measure of tack.

1. 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 more the ball can travel. Quick stick (Peel tack) test: The peel force required for 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. Probe tack test: Force needed to drag a probe away from an adhesive at a fixed rate is recorded as tack.

2. In vitro release studies

The Paddle over Disc: (USP equipment 5/ PhEur 2.9.4.1) This technique is just like the USP paddle dissolution equipment, except that the transdermal system is hooked up to a disc or

cell resting at the bottom of the vessel that contains medium at 32 ±5°C. The Cylinder modified USP Basket: (USP apparatus 6 / PhEur 2.9.4.3) This technique is similar to the USP basket type dissolution apparatus, except that the system is hooked up to the surface of a hollow cylinder immersed in medium at 32 ±5°C.

The reciprocating disc: (USP apparatus 7)

In this technique patches hooked up to holders are oscillated in tiny volumes of medium, allowing the equipment to be helpful for systems delivering low concentration of drug. Additionally paddle over extraction cell technique (PhEur 2.9.4.2) may be used.

In vitro permeation studies:

The quantity of drug available for absorption to the general pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of cuticle through skin appendages. Sometimes permeation studies are performed by inserting the fabricated transdermal patch with rat skin or artificial membrane in between receptor and donor compartment in an exceedingly vertical diffusion cell like Franz diffusion cell or keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic aspect of the membrane and then mounted within the diffusion cell with lipophillic aspect in-tuned with receptor fluid. The receiver compartment is maintained at specific temperature (usually 32±5°C for skin) and is incessantly stirred at a continuing rate. The samples are withdrawn at different time intervals and equal quantity of buffer is replaced eachtime. The samples are diluted suitably and absorbance is determined spectrophotometrically. Then the quantity of drug permeated per centimeter square at each time interval is calculated. Design of system, patch size, surface area of skin, thickness of skin and temperature etc. are some variables that will have an effect on the discharge of drug. Thus permeation study involves preparation of skin, mounting of skin on permeation cell, setting of experimental conditions like temperature, stirring, sink conditions, withdrawing samples at different time intervals, sample analysis and calculation of flux i.e., drug penetrate per cm2 per sec.

Horizontal-type skin permeation system:

This has been widely used for the analysis of drug permeation across skin. The cell is split in receptor and donor compartments with an occasional solution volume (3.5ml) for every compartment and a little membrane space (0.64cm2). They are continuously stirred by matched set of star-head magnets, which are rotated at a speed of 600rpm. The system is controlled by thermostated water through a water jacket surrounding the two compartments.

Franz diffusion cell:

The cell consists of two compartments: donor and receptor. The receptor compartment incorporates a volume of 5-12ml and effective surface area of 1-5 cm2 . The diffusion buffer is unendingly stirred at 600rpm by a magnetic bar. The temperature within the bulk of the solution is maintained by circulating thermostated water through a water jacket that surrounds the receptor compartment.

Flow-through diffusion cell:

Flow through diffusion cells have the advantage that they will be used once the drug has lower solubility within the receptor compartment. This cell will be totally automated and connected on to HPLC. They have giant capability donor chamber to succulent appropriate loading of the applied compound and a low volume (0.3ml) receiving chamber that ensures speedy removal of penetrant at comparatively low pumping rates.

In vivo Studies:

In vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into consideration throughout in vitro studies will be totally explored throughout in vivo studies. In vivo analysis of TDDS will be carried out using animal models human volunteers.

Animal models:

Appreciable time and resources are needed to hold out human studies, so animal studies are most popular at little scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, balding dog, balding Macaca mulatta, rabbit, guinea pig etc. varied experiments conducted lead us to a conclusion

that balding animals are most popular over furry animals in each in vitro and in vivo experiments. Macaca mulatta is one among the foremost reliable models for in vivo evaluation of transdermal drug delivery in man.

Human models:

The ultimate stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic information following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug.

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