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TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT
A transdermal 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. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. The main disadvantage to transdermal delivery systems stems from the fact that the skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered in this method. A wide variety of pharmaceuticals are now available in transdermal patch form.
KEYWORD: *Transdermal Drug Delivery System, Bioavability, Iontophoresis, Electroporation, Ultrasound, Microscopic Projection.*

INTRODUCTION

Transdermal patch (Skin patch) uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch. Drugs administered through skin patches include scopolamine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), and lidocaine to relieve the pain of shingles (herpes zoster). Molecules of insulin and many other substances, however, are too large to pass through the skin. [1]

Patches applied to the skin eliminate the need for vascular access by syringe or the use of pumps. Transdermal patches were developed in the 1970s and the first was approved by the FDA in 1979 for the treatment of motion sickness. It was a three-day patch that delivered scopolamine. In 1981, patches for nitroglycerin were approved, and today there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, oestradiol, oxybutinin, scopolamine, and testosterone. There are also combination patches for contraception, as well as hormone replacement. Depending on the drug, the patches generally last from one to seven days.[2]

The major advantages provided by transdermal drug delivery include the following: improved bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms. Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug-degradation effects. Patches can also reduce side effects; for example, oestradiol patches are used by more than a million patients annually and, in contrast to oral formulations, do not cause liver damage. of two major sub-categories - therapeutic and cosmetic), aroma patches, weight loss patches, and Non-medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists patches that measure sunlight exposure.[2]

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

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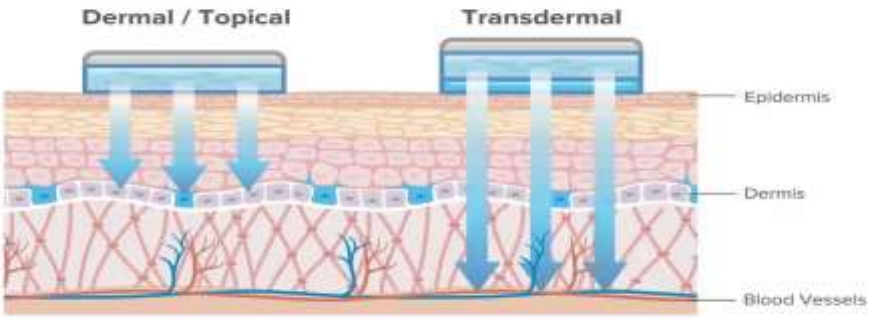

Diagram : Topical and Transdermal Patch

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 dispose of, and there are few or no gastrointestinal effects from the drug itself. Peak plasma levels of the drug are reduced, leading to decreased side effects. In addition, transdermal delivery is useful for those drugs that have a high first pass effect through the liver, have poor oral uptake, need frequent administration, or that interact with stomach acid. The first pass effect results in the destruction of a significant amount of the drug. Drugs absorbed through the skin, however, enter the general circulation directly avoiding the liver, with less total drug absorption occurring.[3]

- Topical patches are a painless, non- invasive way to deliver substances directly into the body.
- Topical patches are a better way to deliver substances that are brokendown by the stomach acids, not well-absorbed from the gut, orextensively degraded by the liver.
- Topical patches over a controlled, steady delivery of medication over longperiods of time.
- Topical patches have fewer side effects than oral medications orsupplements.
- 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 cost-effective.
- People prefer topical patches.

Limitation

- TDDS cannot deliver ionic drugs.
- TDDS cannot achieve high drug levels in blood/plasma.
- It cannot develop for drugs of large molecular size.
- TDDS cannot deliver drugs in a pulsatile fashion.
- DDS 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.[3]

Popular Uses

- The highest selling transdermal patch in the United States 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 (marketed as Duragesic) and Buprenorphine (marketed as BuTrans).
- Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis. Other transdermal patches for hormone delivery include the contraceptive patch (marketed as Ortho Evra or Evra).
- Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.
- The anti-hypertensive drug Clonidine is available in transdermal patch form under the brand 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.[4]

Adverse Events

In 2005, the FDA announced that they were investigating reports of death and other serious adverse events related to narcotic

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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. 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 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 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.[5]

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.

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.[6]

Skin burns have occurred with metal containing transdermal patches at the time of shock therapy from external as well as internal cardioverter defibrillators (ICD).

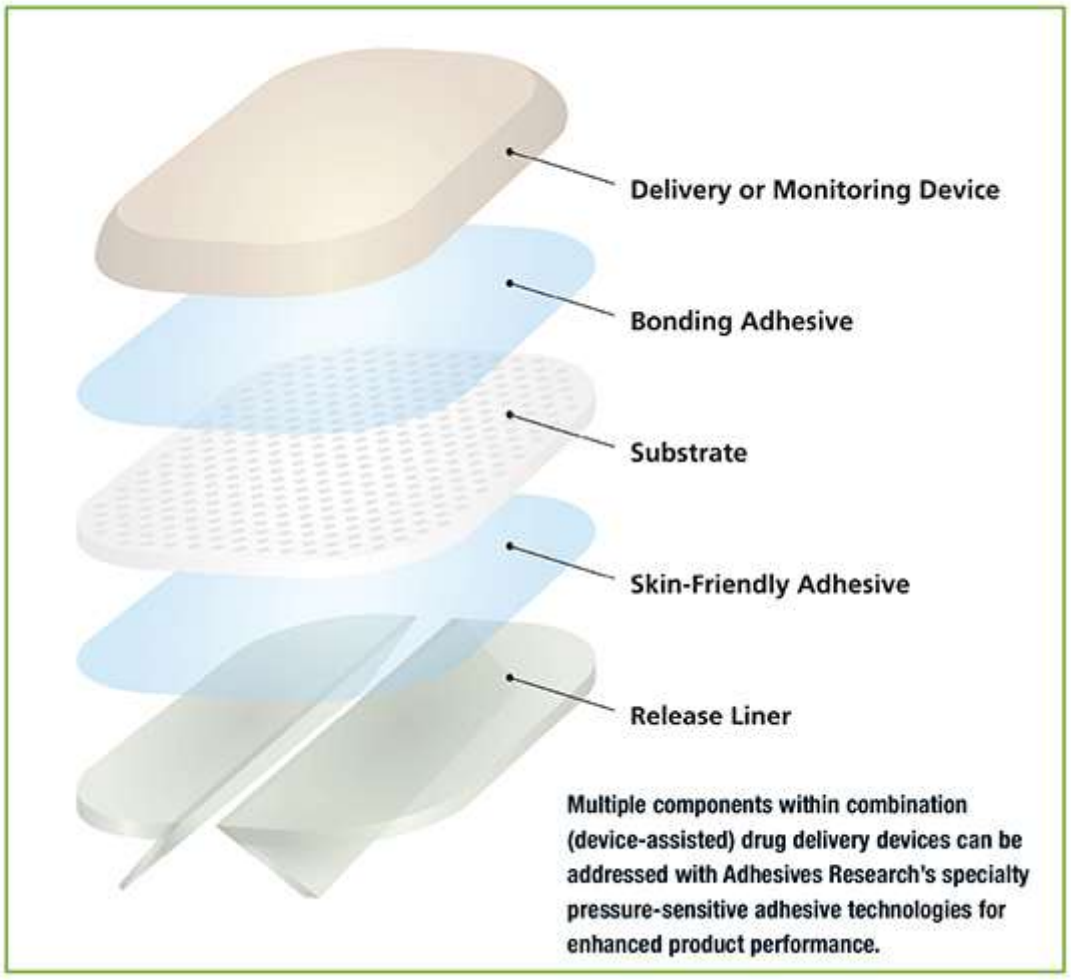

Diagram : Layer of Transdermal Patch

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[5]

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Transdermal patch is used when

1. When the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery.
2. Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia.
3. It can be used in combination with other enhancement strategies to produce synergistic effects.

The use of transdermal patch is not suitable when

(1) Cure for acute pain is required.
(2) Where rapid dose titration is required.
(3) Where requirement of dose is equal to or less than 30 mg/24 hrs.

Factors affecting transdermal bioavaibility

Two major factors affect the bioavaibility of the drug via transdermal routes:
(1)Physiological factors (2) Formulation factors

Physiological factors include

(1)Stratum corneum layer of the skin (2) Anatomic site of application on the body (3) Skin condition and disease (4) Age of the patient (5) Skin metabolism (6) Desquamation (peeling or flaking of the surface of the skin) (7) Skin irritation and sensitization

Formulation Factors Include

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

Care taken while applying transdermal patch

(1)The part of the skin where the patch is to be applied should be properly cleaned. (2) Patch should not be cut because cutting the patch destroys the drug delivery system. (3) Before applying a new patch it should be made sure that the old patch is removed from the site. (4) Care should be taken while applying or removing the patch because anyone handling the patch can absorb the drug from the patch. (5) The patch should be applied accurately to the site of administration.[6]

Mechanism of Action of Transdermal Patch

The 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.

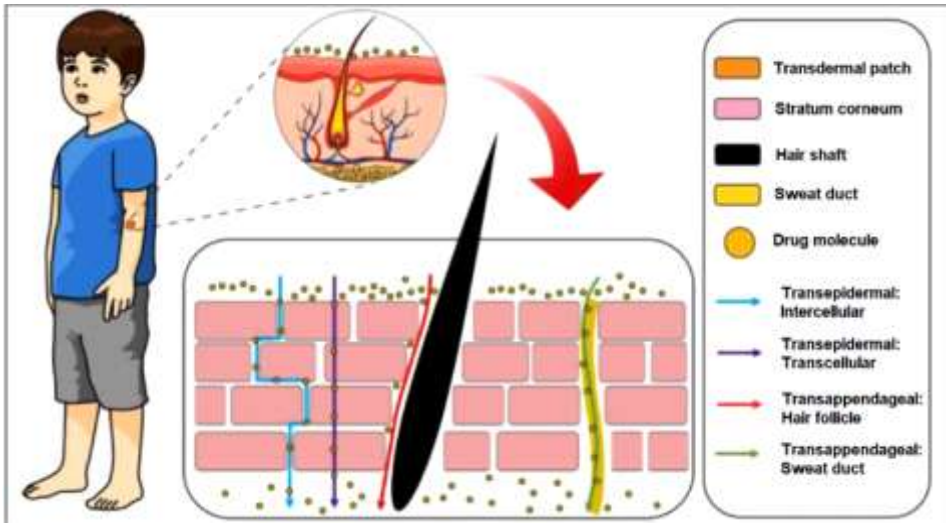

Diagram: Machanism of Action

Iontophoresis

Iontophoresis 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.[7]

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Electroporation
Electroporation 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.[5]

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.

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 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 aid in rapid absorption. They are used in development of cutaneous vaccines for tetanus and influenza.[2]
Various other methods are also used for the application of the transdermal patches like thermal poration, magnetophoresis, and photomechanical waves. However, these methods are in their early stage of development and required further detail studying.

Types of Transdermal Patch
Single-layer Drug-in-Adhesive
The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

Multi-layer Drug-in-Adhesive
The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing.

Reservoir
Unlike the Single-layer and Multi-layer Drug-in- adhesive systems the reservoir transdermal system has 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 also backed by the backing layer. In this type of system the rate of release is zero order

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

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 vapours patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market.[8]

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 different points of the film.

Uniformity of weight: Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

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Drug Content Determination: An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.[8]

Content Uniformity Test: 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in 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 prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula.[9]
% Moisture content = Initial weight – Final weight X 100

Moisture Uptake: Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below.
% moisture uptake = Final weight – Initial weight X 100

Flatness: A transdermal patch should possess a smooth surface and should not constrict with
time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.[8]
% constriction = I1 – I2 X 100 I2 = Final length of each strip I1 = Initial length of each strip

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.

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. The tensile strength can be calculated using the following equation.[8]
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 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.[6]

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

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.

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

In Vitro Release Studies
The Paddle over Disc: (USP apparatus 5/ PhEur 2.9.4.1) This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32 ±5°C.

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

The Reciprocating Disc: (USP apparatus 7) In this method patches attached to holders are oscillated in small volumes of medium, allowing the apparatus to be useful for systems delivering low concentration of drug. In addition paddle over extraction

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cell method (PhEur 2.9.4.2) may be used.[10]

In Vitro Permeation Studies: The amount of drug available for absorption to the systemic 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 epidermis through skin appendages. Usually permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as Franz diffusion cell or keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophillic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature (usually 32±5°C for skin) and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectrophotometrically. Then the amount 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 may affect the release of drug. So 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 permeated per cm2 per sec[10]

Horizontal-Type Skin Permeation System: this has been widely used for the evaluation of drug permeation across skin. The cell is divided in receptor and donor compartments with a low solution volume (3.5ml) for each compartment and a small membrane area (0.64cm^2). 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.[9]

Franz Diffusion Cell: the cell is composed of two compartments: donor and receptor. The receptor compartment has a volume of 5-12ml and effective surface area of 1-5 cm2. The diffusion buffer is continuously stirred at 600rpm by a magnetic bar. The temperature in 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 can be used when the drug has lower solubility in the receptor compartment. This cell can be fully automated and connected directly to HPLC. They have large capacity donor chamber to aloe appropriate loading of the applied compound and a low volume (0.3ml) receiving chamber that ensures rapid removal of penetrant at relatively low pumping rates.[10]

In Vivo Studies: In vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using animal models human volunteers.

Animal Models: Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted leadus to a conclusion that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments. Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in man.[9]

Human Models: The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data 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.[9]

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