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TRANSDERMAL PATCHES : A REVIEW

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ABSTRACT

Transdermal patches have been available on the global market for more than 25 years as a successful alternative to systemic drug delivery for selected drug molecules, and are known as Transdermal Drug Delivery Systems (TDDS). They are also known as Transdermal Therapeutic Systems, abbreviated as TTS. The drug delivery mechanism is the passive diffusion of drug across the skin from this adhesive transdermal patch. Despite the relatively higher costs, the transdermal patches have proved advantageous for delivery of selected drugs, such as estradiol, ethinyl estradiol, clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, norethindrone acetate, norelgestromin, oxybutynin, prilocaine, scopolamine, and testosterone. Since the first transdermal patch, scopolamine was approved in 1979 all the drug molecules mentioned above are available as approved transdermal products in American and European market. In India TD patches containing active drug molecule such as nicotine, estradiol, fentanyl, glyceryl trinitrate, and testosterone are available. Transdermal patches are utilized for mainly hormonal therapy, narcotic analgesia, antihypertensive & anti-emetic therapies, and smoking deterrent. Transdermal patches offer superior uniformity of drug concentrations in plasma throughout their duration of use. This results in reduced side effects and, sometimes, improved efficacy over other dosage forms.

Key words *Transdermal patch, Preparation of transdermal patch, Evaluation of transdermal patch.*

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INTRODUCTION

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 by this method. A wide variety of pharmaceuticals are now available in transdermal patch form.[1,2]

TYPES:-

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.One of the layers is for immediate release of the drug and other layer is for control release of drug from the reservoir. 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. Also known as a monolithic device

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.[3]

PREPARATION OF DIFFERENT TYPES OF TRANSDERMAL PATCHES:-

Several system designs have been used in development and fabrication of TDDSs. The systems that have been introduced in market can be classified into following types [4,5]

Matrix Type Transdermal Patch(s):

Drug reservoir is prepared by dissolving the drug and polymer in a common solvent. The insoluble drug should be homogenously dispersed in hydrophilic or lipophillic polymer. The required quantity of plasticizer like dibutylpthalate, triethylcitrate, polyethylene glycol or propylene glycol and permeation enhancer is then added and mixed properly. The medicated polymer formed is then molded into rings with defined surface area and controlled thickness over the mercury on horizontal surface followed by solvent evaporation at an elevated temperature. The film formed is then separated from the rings, which is then mounted onto an occlusive base plate in a compartment fabricated from a drug impermeable backing. Adhesive polymer is then spread along the circumference of the film. [6,7]

The dispersion of drug particles in the polymer matrix can be accomplished by either homogenously mixing the finely ground drug particles with a liquid polymer or a highly viscous

base polymer followed by cross linking of polymer chains or homogenously blending drug solids with a rubbery polymer at an elevated temperature.[8]

Reservoir Type Transdermal Patch(s):

The drug reservoir is made of a homogenous dispersion of drug particles suspended in an unleachable viscous liquid medium (e.g. silicon fluids) to form a paste like suspension or gel or a clear solution of drug in a releasable solvent (e. g. ethanol). The drug reservoir formed is sandwiched between a rate controlling membrane and backing laminate.[9] The rate controlling membrane can be nonporous so that the drug is released by diffusing directly through the material, or the material may contain fluid filled micropores in which case the drug may additionally diffuse through the fluid, thus filling the pores.

Rate controlling membrane may be prepared by solvent evaporation method or compression method. In case of solvent evaporation method, polymer is dissolved in solvent with or without plasticizer.[10] Then the solution is poured on the horizontal surface and left for evaporation of solvent in order to obtain a thin film. In case of compression method, polymer is compressed with required force at high temperature for specific period of time.[11] Drugs that require relatively high doses or greater permeation enhancement, such as testosterone, use liquid reservoir systems. But the application of enhancers and adhesive technologies has allowed many drugs that were initially administered in liquid reservoirs to be used as matrix type systems e.g. estradiol, nicotine, nitroglycerine. The main advantage of reservoir type patches is that this patch design can provide a true zero order release pattern to achieve a constant serum drug level.[12]

Membrane matrix hybrid type patch(s):

This is the modification of reservoir type transdermal patch. The liquid formulation of the drug reservoir is replaced with a solid polymer matrix (e.g. polyisobutylene) which is sandwiched between rate controlling membrane and backing laminate.[13]

Micro reservoir type transdermal patch(s):

The drug reservoir is formed by suspending the drug solids in an aqueous solution of water miscible drug solubilizer e.g. polyethylene glycol. The drug suspension is homogenously dispersed by a high shear mechanical force in lipophillic polymer, forming thousands of unleachable microscopic drug reservoirs (micro reservoirs). The dispersion is quickly stabilized by immediately cross linking the polymer chains in-situ which produces a medicated polymer disc of a specific area and fixed thickness. Occlusive base plate mounted between the medicated disc and adhesive form backing prevents the loss of drug through the backing membrane.[14,15]

Drug in adhesive type transdermal patch(s):

The drug and other selected excipients, if any, are directly incorporated into the organic solvent based pressure sensitive adhesive solution, mixed, cast as a thin film and dried to evaporate the solvents, leaving a dried adhesive matrix film containing the drug and excipients. This drug in adhesive matrix is sandwiched between release liner and backing layer. Drug -in -adhesive patch may be single layer or multilayer. The multilayer system is different from single layer in that it adds another layer of drug-in-adhesive, usually separated by a membrane.[16]

APPLICATIONS:-[17,18,19,20,21]

1. 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.
2. Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl and Buprenorphine.
3. 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 and testosterone patches for both men and women.
4. Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.

5. Transdermal scopolamine is commonly used as a treatment for motion sickness.
6. The anti-hypertensive drug Clonidine is available in transdermal patch form under the brand name Catapres-TTS.

EVALUATION OF TRANSDERMAL PATCHES:-[22]

a) Physicochemical evaluation
b) In vitro evaluation
c) In vivo evaluation

Physicochemical Evaluation*:*

- **Thickness:** The thickness of transdermal film is determined by traveling 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.
- **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.
- **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.

  % Moisture content = Initial weight – Final 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 / 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.

  % constriction = $I_1 – I_{2/} I_1$ X 100

  I_2 = Final length of each strip

  I_1 = Initial length of each strip
- **Adhesive studies:**

  The therapeutic performance of TDDS can be affected by the quality of contact between the patch and the skin. The adhesion of a TDDS to the skin is obtained by using PSAs, which are defined as adhesives capable of bonding to surfaces with the application of light pressure. The adhesive properties of a TDDS can be characterized by considering the following factors.
- **Peel Adhesion properties**: It is the force required to remove adhesive coating from test substrate. It is tested by measuring the force required to pull a single coated tape, applied to substrate at 180° angle. The test is passed if there is no residue on the substrate.
- **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.

- **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.
- **Shear strength properties or creep resistance** : Shear strength is the measurement of the cohesive strength of an adhesive polymer *i.e.*, device should not slip on application determined by measuring the time it takes to pull an adhesive coated tape off a stainless plate.

b) In vitro release studies:

Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms and hence their in vivo performance. A number of mathematical model have been developed to describe the drug dissolution kinetics from controlled release drug delivery system *e.g.*, Higuchi, First order, Zero order and Peppas and Korsenmeyer model. The dissolution data is fitted to these models and the best fit is obtained to describe the release mechanism of the drug.

There are various methods available for determination of drug release rate of TDDS.

- **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 cell method (PhEur 2.9.4.2) may be used.
- **Diffusion Cells e.g. Franz Diffusion Cell and its modification Keshary- Chien Cell**: In this method transdermal system is placed in between receptor and donor compartment of the diffusion cell. The transdermal system faces the receptor compartment in which receptor fluid *i.e.,* buffer is placed. The agitation speed and temperature are kept constant. The whole assembly is kept on magnetic stirrer and solution in the receiver compartment is constantly and continuously stirred throughout the experiment using magnetic beads. At predetermined time intervals, the receptor fluid is removed for analysis and is replaced with an equal volume of fresh receptor fluid. The concentration of drug is determined spectrophotometrically.

  The pH of the dissolution medium ideally should be adjusted to pH 5 to 6, reflecting physiological skin conditions. For the same reason, the test temperature is typically set at 32°C (even though the temperature may be higher when skin is covered). PhEur considers 100 rpm a typical agitation rate and also allows for testing an aliquot patch section. The latter may be an appropriate means of attaining sink conditions, provided that cutting a piece of the patch is validated to have no impact on the release mechanism. The dissolution data obtained is fitted to mathematical models in order to ascertain the release mechanism.

- **In vitro permeation studies:**
  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. 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.
- **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 lead us 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.

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.

Skin irritation studies:

White albino rats, mice or white rabbits are used to study any hypersensitivity reaction on the skin. The mice were divided into 5 groups, each group containing 6 animals. On the previous day of the experiment, the hair on the backside area of mice were removed. The animals of group I was served as normal, without any treatment. One group of animals (group II, control) was applied with marketed adhesive tape (official adhesive tape in USP). Transdermal systems (blank and drug loaded) were applied onto nude skin of animals of III and IV groups. A 0.8% v/v aqueous solution of formalin was applied as standard irritant (group V). The animals were applied with new patch/ formalin solution each day up to 7 days and finally the application sites were graded according to a visual scoring scale, always by the same investigator. The erythema was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for scar formation. The edema scale used was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for severe. After visual evaluation of skin irritation, the animals were sacrificed and skin samples were processed for histological examination. The results of this study showed that the prepared systems (both blank and drug loaded) and USP adhesive tape produced negligible erythema and edema. While standard irritant, formalin produced severe edema and erythema. The histopathologic examination of the skin also indicated that adhesive tape and prepared patches produced mild inflammation and edema.

Stability studies:

The stability studies are conducted to investigate the influence of temperature and relative humidity on the drug content in different formulatiosns. The transdermal formulations are subjected to stability studies as per ICH guidelines.

Regulatory requirements:

A transdermal patch is classified by U.S. Food and Drug Administration (FDA) as a combination product, consisting of a medical device combined with drug or biologic product that the device is designed to deliver. Prior to sale, any transdermal patch product must receive approval from FDA, demonstrating safety and efficacy for its intended use.

CONCLUTION:-

Since 1981, transdermal drug delivery systems have been used as safe and effective drug delivery devices. Their potential role in controlled release is being globally exploited by the scientists with high rate of attainment. A transdermal patch has several basic components like drug reservoirs, liners, adherents, permeation enhancers, backing laminates, plasticizers and solvents, which play a vital role in the release of drug via skin. Transdermal patches can be divided into various types like matrix, reservoir, membrane matrix hybrid, micro reservoir type and drug in adhesive type transdermal patches and different methods are used to prepare these patches by using basic components of TDDS

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