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TRANSDERMAL DRUG DELIVERY PATCHES: A REVIEW

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ABSTRACT

Transdermal drug delivery is a topical drug delivery. This drug delivery system was studied to overcome the drug delivery difficulties specially oral route of drug administrations. A transdermal patch is adhesive patch which is placed on human skin to drug delivery of medication into bloodstream via human skin. The injured area of human body promotes healing by this drug delivery. Transdermal patch provides controlled release medication into patients. The human skin is effective barrier to deliver dose of drug. Small molecules of drug easily penetrate the skin. The overall introduction of transdermal drug delivery system i.e. skin anatomy, method of preparation, factors affecting, and evaluation is described in this review article.

Keywords: Transdermal, permeation pathway, permeation enhancer

INTRODUCTION

Transdermal patch refers to topical application delivery agent to skin. Transdermal patch has many advantages over the conventional dosage forms. In transdermal drug delivery system, Transdermal patch provides constant blood levels, avoidance of first pass metabolism, patient compliance, and avoidance of dose dumping. Transdermal drug delivery is self contained drug delivery which is used as topical application of dose of drug. This drug delivery system provides drug release constant but allows to continuously short biological half life of drug. Transdermal drug

delivery system enables to avoid GI absorption, which is associated with enzymatic pitfalls and pH deactivation. Transdermal drug delivery offers many advantages i.e. constant maintenance, prolonged drug dose level, reduced frequency of drug dose, self-administration, and easy termination of drug.

Advantages-

1. Self administration is possible.
2. It is convenience.
3. Improved patient's compliance.
4. There is no interaction with gastrointestinal fluids.
5. Its reduced side effects.
6. It reduces first pass metabolism effects.
7. Sustains therapeutic drug level.
8. This is non-invasive i.e. no needles or any injections.
9. It has long acting drug delivery.
10. It can be helps to investigation of skin permeation mechanisms of drug before developed in transdermal delivery.
11. In this system, reasonable constant dosage can be maintained.
12. Easy to apply and remove.
13. Easy elimination of drug delivery during toxicity.

Disadvantages-

1. Possibility of local irritation at the site of application.
2. Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation.
3. May cause allergic reactions.
4. A molecular weight less than 500 Da is essential.
5. Sufficient aqueous and lipid solubility, a log P /water) between 1 and 3 is required for permeate to transverse SC and underlying aqueous layers.

Anatomy of skin:

The anatomy of skin structure is studied for understanding the environment provided for delivering drugs. Transdermal route provides drug absorption via the skin. By this route many more advantages over other routes of administrations [1, 2].

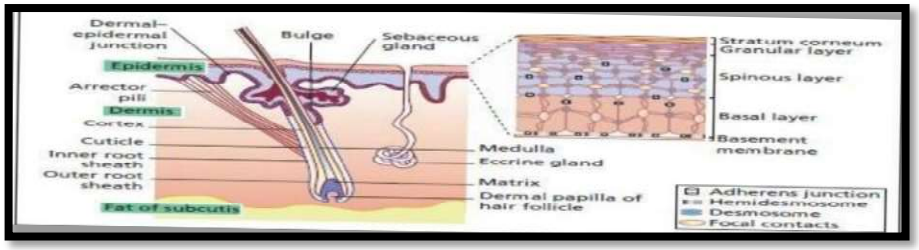

Figure 1: Anatomy of skin

Human skin:-

The skin plays an important role in the transdermal drug delivery system. The skin of an average adult body covers a surface area of approximately 2 sq. m. and receives about one third of the blood circulating through the body and serves as a permeability barrier against the transdermal absorption of various chemical and biological agent. The main three layers of skin play an important role in transdermal drug delivery system.

Structure of skin:

The skin structure comprises three layers accompanied by,

- **Epidermis-** This is the skins outermost layer. Its provide waterproof barrier and skin tone.it is divided into 5 subparts i.e. Stratum corneum, stratum lucidum, stratum granuloma, strartum spinosum, stratum basal.
- **Dermis-** Tightly connected to the epidermis by basement membrane. this is a beneath of skin layer epidermis consist of epithelial tissues. Dermis consist of two areas,i.e. papillary region and reticular region.
- **Hypodermis**- Lower section of the skin structure.

Ideal molecular properties for transdermal drug delivery.

From the above considerations we can conclude with some observations that can termed as ideal molecular properties for drug penetration. They are as follows.

- An adequate solubility in lipid and water is necessary for better penetration of drug (1 mg/ml).
- Optimum partition coefficient is required for good therapeutic action.
- Low melting point of drug is desired (<200°C).
- The pH of the saturated solution should be in between 5 to 9.

Methods for Enhancing Transdermal Drug Delivery

MECHANISM OF ACTION OF PENETRATION ENHANCERS:-

Different Penetration Enhancers have different mechanism of action. The miscibility and solution properties of enhancers can responsible for enhanced transdermal delivery of water soluble drugs. Mechanisms for penetration enhancement of oil soluble drugs are due to partial leaching of epidermal lipids by this improvement of drug permeation through skin. To increase penetration of lipophilic compounds for this necessary to modify partitioning characteristics at the stratum corneum at viable tissue interface. This may be possible by

combining a penetration enhancer with a co-solvent. Some enhancers cause keratin to swell and leach out essential structural material from the stratum corneum thus reducing the diffusion resistance and increasing the permeability. Some penetration enhancers cause change in the protein conformation.

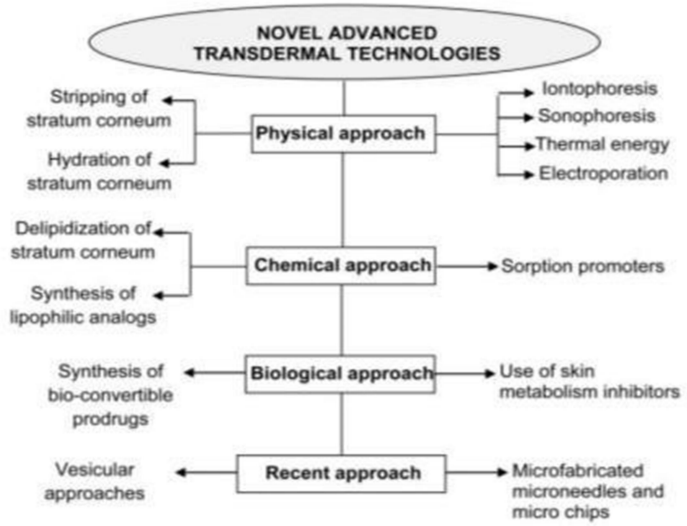

Figure 2: Mechanism Of Action Of Penetration Enhancers

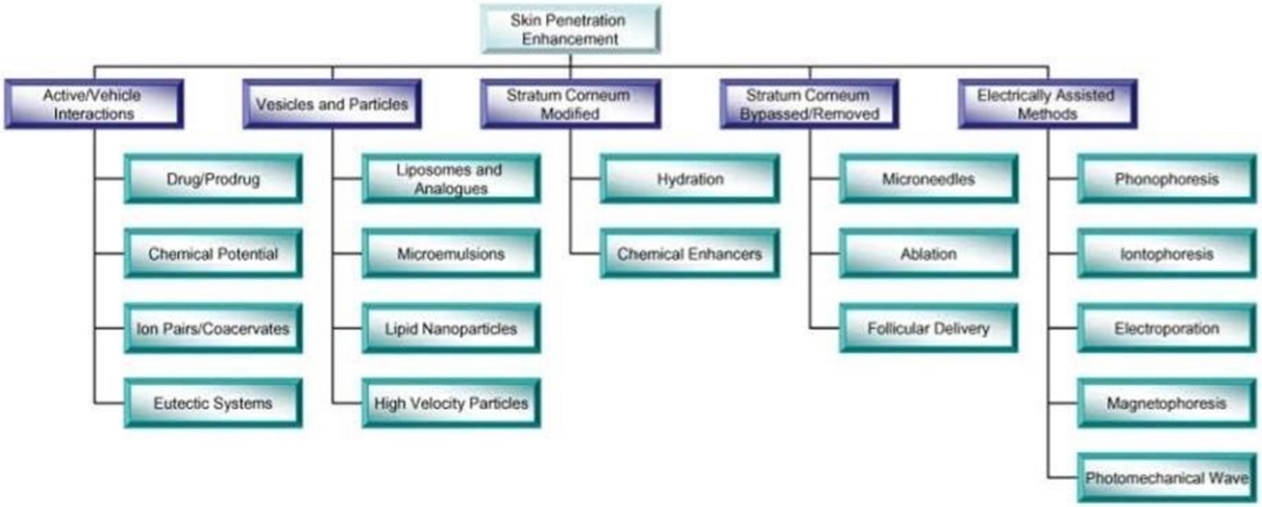

Figure 3: Various Techniques of Skin Permission Enhancement

Skin penetration can be enhanced by following methods:

1) Drug/Prodrug:

Prodrugs are therapeutically inactive derivatives of therapeutically active drugs. prodrug undergoes metabolism to produce the therapeutically active drug A prodrug is

more lipophilic than the parent drug and has different physicochemical [18].Different prodrugs were developed for estradiol and "Transdermal Bioactive Hormone Delivery devices were developed based on the results. The elapse ate of estradiol from Transdermal Bioactive Hormone Delivery is dependent on the chain lerugth of the ester group at the 17 position[19]Alkyl ester prodrugs of ketorolac having optimum lipophilic could improve the transdermal delivery of ketorola[20.]Also, the prodrug approach is every feasible way to Increase the skin permeation of protein/peptidedrug[21].

2)**Eutectic System:**

A eutectic system is a mixture of chemical compounds composition that solidifies at a lower temperature than any other or elements that has a single chemical composition. According According to regular solution theory, the lower the melting point, the greater the solubility of a material in a given solvent, including skin lipids. The melting point of a drug delivery system can be lowered EMLA cream, a formulation consisting of a eutectic mixture of lignocaine and procaine applied under an occlusive film, provides effective local anesthesia for pain-free venipuncture and other procedure [22, 23]

2) Liposomes and Analogues:

Liposomes are colloidal particles formedas concentric bimolecular layers that are capable of encapsulatingdrugs. There are many examples of cosmetic products in which the active ingredients are encapsulated in vesicles. These include humectants such as glycerol and urea, unscreening and tanning agents, enzymes, etc. Phosphatidylcholine from soybean or egg yolk is the most common composition although many other potential ingredients have been evaluated.[23] Cholesterol added to the composition tends to stabilize the structure thereby generating more rigid liposomes. The mechanism of enhanced drug uptake into the stratum corneum is unclear. It is possible that the liposomes either penetrate the stratum corneum to some extent then interact with the skin lipids to release their drug or that only their components enter the stratum corneum.

3) Skin hydration:

Permeability varies according to skin condition. Hydrated skin is more permeable than dry skin. Hydration of skin reduces resistance by loosening the packaging of layers of stratum corneum.

4) chemical enhancer:

Incorporation of penetration enhancers facilitates the absorption of drugs by altering the barrier property of the stratum corneum. A permeation enhancer

should be pharmacologically inert, nontoxic, nonirritating, no allergic, odorless, tasteless, colorless, comparible with most drug and excipients, inexpensive, and have good solvent properies.[27] Different classes of penetration enhancers including alcohols and polyols (ethanol, propylene goal), surfactants (Tween, Span, SL5), fatty acids (Oleic acid), amines and unmakes (Acne, Nmethylpyrolidone), terpenes (irmonene) sulfoxides (dimethyl-sulfosixde), esters (isopropylmyristate) were developed over the past two decades. [28,29]Permeation enhances can enhance the skin permeability by a variety of mechanisms, including interaction with intercellular lipids leading to disruption of their organization and increasing their fluidity. [30]extraction of lipids from the stratum corneum, displacement of bound water, loosening of horny cells, delamination of stratum corneum enhancing solubility and increasing partitioning into the stratum corneum interaction.[31]with intercellular protein, and keratin denaturation.[32]

5) Microniddle:

Transdermal patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. Needles ranging from approximately 10-100 jum 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 penetrationor 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.

6) Abrasion:

The abrasion technique involves the direct removal or disruption of the upper layers of the skin. These devices are based on techniques employed by dermatologists for superficial skin resurfacing which are used in the treatment of acne, scars, hyperpigmentation and other skin blemishes.

7) Phonoporosis:

This technique involves the use of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or via pretreatment. It uses low frequency ultrasound (55 kHz) for an average duration of 15 seconds to enhance skinpermeability.[25]

8) Iontophorosis:

Iontophoresis passes a few mill amperes 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. Iontophoresis enhances drug delivery across the skin by two principal mechanisms: Electrorepulsion and electro osmosis. Electrorepulsion is the direct effect of the applied electric field on a charged permanent. The second mechanism, electro-Osmosis, and results from the tact that the skin supports a net negative charge at physiological pH. lontophoresis is a non invasive method used to boost high concentration of a charged substance, generally medication or bioactive agents, transdermally by repulsive electromotive force using a small electrical current applied to an Iontophoresis chamber containing a similarly charged active agent and its vehicle. These movements are measured in units of chemical flux, commonly jumol/em h. This technique is based on the general principle that like charges repel each other. Thus, during lontophoresis, if delivery of a positively charged drug (D) is desired, the charged drug is dissolved in the electrolyte surrounding the electrode of similar polarity, i.e. the anode in this example. Mainly used for pilocarpine delivery to induce sweating as part of cystic fibrosis diagnostic test. lontophoretic delivery of lidocaine appears to be a promising approach for rapid onset of anesthesia [24]

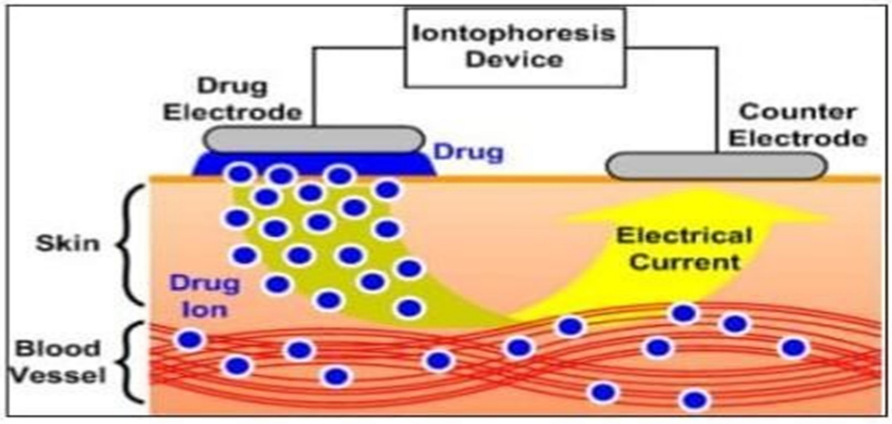

Figure 4: Iontophoresis

9) Electroporation:

Electroporation is a method of application of short, high-voltage electrical pulses to the skin. After electroporation, the permeability of the skin tor diffusion of drugs is increased by 4 orders of magnitude. The electrical pulses are believed to tormtransient aqueous pores in the stratum corneum, through which drug

transport occurs. It is safe and the electrical pulses can beadministered painlessly using closely spaced electrodes to constrain the electric field within the nerve-free stratum corneum.

10) Magnetophorosis:

It involves application of magnetic field that acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin. Skin exposure to a magnetic field might also induce structural alterations that could contribute to an increase in permeability.[26]

11) Photochemical wave:

Lasers arefrequently used for treatment of dermatological conditions like acneand to confer facial rejuvenation. This method involves direct andcontrolled exposure of a laser to the skin that results in the ablation.[24]

12) Application of pressure:

The application of modest pressure i.e25kPa provides a potentially non-invasive and simplest method of skin permeability of molecules such as caffeine.

Basic components used in transdermal patch formulation:

a) Ideal properties of drug:

a) Polymer matrix / drug reservoir
b) Drug
c) Permeation enhancer
d) Pressure sensitive adhesives (PSA)
e) Backing laminate
f) Release liner
g) Plasticizers and solvents

A) **Polymer matrix / drug reservoir:** It is prepared by liquid or solid state synthetic polymer base. It should have biocompatibility and chemical compatibility with the drug.

Polymers used in transdermal drug delivery system are classified as:

1) **Natural polymer**: cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan, etc.
2) **Synthetic elastomers**: polybutadiene, hydrin rubber, silicon rubber, acrylonitrile, neoprene, butyl rubber.
3) **Synthetic polymers**: polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyurea.

B) Drug: Consider some ideal properties and factors of drug for preparation of transdermal patches.

Table 1: Ideal Properties Of Drug

Sr. no.	Parameter	Properties
1	Dose	Should be low in wt. (less than 20 mg/day)
2	Half-life	10/less (hrs.)
3	Molecular wt.	<400da
4	Skin permeability coefficients	>0.5*10-3cm/h
5	Skin reaction	Non irritating, non sensitizing
6	Oral bioavailability	Low

b) Factors affecting:

Table 2: Factor Affecting

Physicochemical	Pharmacokinetics	Biological
Solubility	Half-life	Skin toxicity
Crystallinity	Volume of distribution	Site of application
Molecular wt.	Total body clearance	Allergic reaction
Polarity	Therapeutic plasma conc.	Skin metabolism
Melting point	Bioavailable factor	

Permeation enhancers:

These are the compounds, which promote skin permeability by altering the as a barrier to the flux of a desired penetrant and are considered as an integral part of most transdermal formulations. To achieve and maintain therapeutic concentration of drug in the blood, the resistance of skin to diffusion of drugs has to be reduced in order to allow drug molecules to cross skin and to maintain therapeutic levels in blood. They can modify the skin's barrier to penetration either by interacting with the formulation that applied or with the skin itself. The penetration enhancer should be pharmacologically inert, non toxic, non allergenic, non-irritating and ability to act specifically, reversibly and for predictable duration. It should not cause loss of body fluids, electrolytes or other endogenous materials. these conveniently classified under the following main heading:

1. Solvents
2. Surfactant
3. Bile salt
4. Miscellaneous chemicals.

1.Solvent:

These compounds increase penetration possibly by

1) Swelling the polar pathways in the skin.

2) Fluidization of lipids.

Examples: Examples include water alcohols-methanol and ethanol; alkyl methyl sulfoxidesdimethyl sulfoxide, alkyl homologs of methyl sulphoxide, dimethy acetamide and dimethyl formamide; pyrrolidones-2-pyrrolidone; laurocapram solvents-propylene glycol, glycerol, silicone fluids, isopropyl palmitate. (Azone),

2.Surfactants

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the head group and the hydrocarbon chain length. These compounds are skin irritants, therefore, a balance between penetration enhancement and irritation have to be considered. Anionic surfactant can penetrate and interact strongly with the skin. Once these surfactants have penetrated the skin, they can induce large alterations. Cationic surfactants are reportedly more irritant than the anionic surfactants and they have not been widely studied as skin permeation enhancers. Of the three major classes of surfactants, the nonionic have long been recognized as those with the least potential for irritation and have been widely studied.

Examples of commonly used surfactants are:

Anionic Surfactants:

Sodium lauryl sulphate, Dioctylsulphosuccinate, Decodecylmethylsulphoxide etc.

Nonionic Surfactants:

Plutonic F127, Plutonic F68, etc. Bile Salts: Sodiumtaurocholate, Sodium doctorate, Sodium tauroglyco Plutonic

3. Bile salt: Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate

4. Miscellaneous Chemicals:

These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-polyamide; Calcium thioglycolate; Anticholinergic agents. Some potential permeation But enhancers have recently been described the available data on their effectiveness are sparse. These include eucalyptol. dio-methyl-beta-cyclodextrin and soya bean casein.

Ideal properties: i) They should be free from irritating, toxic and allergy.

ii) They not bind to receptor site.

iii) Should be cosmetically acceptable with an appropriate skin feel.

c)**Pressure sensitive adhesives**:

It is increase the adherence of transdermal patch on the human skin surface. It can easily remove from the human skin surface without residue leave on it.

a) Polyacrylates

b) Polyisobutylene

c) Silicon based adhesives

e) Backing laminate: It is a supportive material. It is chemically compatible with the drug, enhancer, adhesive and other excipients. Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is impermeable and protects the product during use on the skin e.g. metallic

plastic laminate, plastic backing with absorbent pad and occlusive base plate a (aluminum foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminum foil disc)[3,4]

f) Release liner: It is the primary packaging material. It is made up of Non-occlusive OR Occlusive base layer. During storage release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. The release liner is composed of a base layer which may be non-occlusive (paper fabric) or occlusive (polyethylene, polyvinylchloride) and a release coating layer made up of silicon or Teflon. Other materials used for TDDS release liner include polyester foil and metalized laminate.[5, 6]

g) Plasticizers and solvents:

a) Solvents: Chloroform, methanol, acetone, isopropanol.

b) Plasticizers: dibutylpthalate, triethylcitrate, polyethylene glycol, propylene glycol.

DESIGN OF TRANSDERMAL DELIVERY SYSTEM:

The basic components of any transdermal delivery system include the drug dissolved or dispersed in an inert polymer matrix that provides support and platform for drug release. There are two basic designs of the patch system that dictate drug release characteristics and patch behavior:

1) Matrix or Monolithic:

The inert polymer matrix binds with the drug and controls its release from the device.

2) Reservoir or Membrane:

The polymer matrix does not control drug release. Instead, a rate controlling membrane present between the drug matrix and the adhesive layer provides the rate limiting barrier for drug release from the device.

Methods of preparation of TDDS:

1) **Mercury substrate method**:

In this method amount of drug dissolved in amount of polymer solution with plasticizer. The stirr above solution until production of homogenous dispersion and kept side to removed air bubbles completely and then poured into a glass ring. The rate of solvent evaporation controlled by placing an inverted funnel over the petri dish. After that the films stored in a desiccator.[16]

2) **Glass substrate method:**

The polymeric solutions are kept a side for swelling and add plasticizer. Then add drug solution and stirred for 10 min. After that solution kept aside to remove air bubbles and then poured in a clean petriplate. The

solvent evaporation rate is controlled by placing an inverted funnel over the petri dish. After 24 hrs, taken out dried films and stored in desiccator.[3-9]]

3) **Asymmetric TPX membrane method:**

A prototype patch fabricated by a heat sealable polyester film with a concave of 1cm diameter. Heat sealable polyester film is used as the backing membrane. It's covered by TPX asymmetric membrane, and sealed with an adhesive.[9]

4) **By using IPM membranes method:**

In this method drug is dissolved in a mixture of water and propylene glycol and stirred for 12 hrs. with the help of magnetic stirrer. The dispersion is neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used to obtain solution gel. Incorporate formed gel in the IPM membrane.

Evaluation of transdermal drug delivery system:

1. **Physical appearance-**

Check color, clarity, entrapment of air bubbles, flexibility, and smoothness of all prepared patches visually. [8]

2. **Thickness-**

By using vernier calliper, the thickness of patches tested. Checked thickness of patch from each batch and average thickness was determined. The thickness of the drug loaded patch is measured in different points by using a digital micrometer and the average thickness and standard deviation is determined to ensure the thickness of the prepared patch. The thickness of transdermal film is determined by traveling microscope dial gauge, screw gauge or micrometer at different points of the film [11, 20.]

3. **Weight variation:**

Prepared patch dried before testing. Specified area of patch to be cut in different parts of patch and weighed. Average weight calculated. The prepared patches are dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

4. **Flatness:**

Three strips cut from each portion of patch i.e. center strips, left and right side strips. Measured length of each strips. Non-uniformity in flatness was measured by percent constriction with 0% to 100% flatness.[12]

5. **Folding endurance-**

Strip of patch to be cut evenly and repeatedly folded at the same place till it broke. The no of times of folding without breaking is the value of folding endurance..A

strip of specific area is to be cut evenly and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.[12]

6. Drug content-

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples.[13]

Percentage moisture loss-

Weighed patch kept in desiccators at room temp. for 24 hrs. after 24 hrs. patch reweighed and determine percent moisture loss. The prepared films are to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs. the films are to be reweighed and determine the percentage moisture content from the below mentioned formula [14]

%Moisture loss= (Initial wt. – Final wt. / Final wt.)×100

7. In-vitro drug release studies-

The paddle over disc method (USP apparatus V) used for In-vitro drug release studies of patches. Patch cut and placed on glass plate. Glass plate placed into dissolution medium and apparatus equilibrated to 37±0.5◦c.

The distance between paddle and glass plate was set 2.5cm and operated at 50 rpm. Sample withdrawn at appropriate time interval up to 24 hrs. and analyzed by UV spectrophotometer[15.]

9. Skin Irritation study -

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury. [16]

10. Stability studies

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months. The samples are withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.[21]

11. 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.

12.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.

14.Thumb tack test:

The force required to remove thumb from adhesive is a measure of tack.

15.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.

16.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.

17.Probe tack test:

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

APPLICATION

1. Transdermal patch of nicotine, which releases nicotine in controlled doses to help with cessation of tobacco smoking.

2.. Nitroglycerine patches are also sometimes prescribed for the treatment of Angina

3. Clonidine, the antihypertensive drug and ketoprofen, the non-steroidal anti-Inflammatory. drug is also available in the form of transdermal patches
4. Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD).

FUTURE OF TRANSDERMAL THERAPY:

Ten years ago, the nicotine patch had revolutionized smoking cessation; patients were being treated with nitroglycerin for angina, clonidine for hypertension, scopolamine for motion sickness and estradiol for estrogen deficiency, all through patches. At that time, biotech medicinal was still being developed. During the past decade, the number of drugs formulated in the patches has hardly increased, and there has been little change in the composition of the patch systems. Modifications have been mostly limited to refinements of the materials used. The reason is the only a limited number of drugs fit the molecular weight, and potency requirements for transdermal absorption.

CONCLUSION

Transdermal drug delivery is a painless, convenient, and potentially effective way to deliver regular doses of many medications. Wide range of drugs can be delivered improved drug uptake Minimal complications and side effects low cost and easy to use. Example Ten years ago, the nicotine patch had revolutionized smoking cessation; patients were being treated with nitroglycerin for angina, clonidine for hypertension, scopolamine for motion sickness and estradiol for estrogen deficiency, all through patches used by over a million patients per year. Transdermal delivery of a drug product which is currently approved as oral dosage form, allows for the avoidance of first pass metabolism. Dermal patches are the most common form of transdermal delivery of drugs. However, the transdermal technologies have limitations due to the relatively impermeable thick of outer stratum corneum layer. Researchers are trying to overcome this hurdle of poor permeability by physical and chemical means.

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