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Review Article

TRANSDERMAL DRUG DELIVERY SYSTEM (PATCHES), APPLICATIONS IN PRESENT SCENARIO

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ABSTRACT

Transdermal drug delivery system are topically administered medicaments. Transdermal patches are pharmaceutical preparation of varying sizes, containing, one or more active ingredient, intended to be applied to the unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers, and it avoid first pass effect. Transdermal patches delivers the drugs for systemic effects at a predetermined and controlled rate. Through a diffusion process, the drug enters the bloodstream directly though the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow. Characterization of transdermal patch is use to check it's quality, size, time of onset & duration, adhesive property, thickness, weight of patch, moisture of content, uniformity & cutaneous toxicological studies. The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally.

Keywords: Transdermal patches, marketed TDD, Diffusion.

INTRODUCTION

The most common[8], form of delivery of drugs is the oral route. It has the notable advantage of easy administration, but also have significant drawbacks – namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and / or frequent dosing, which can be both cost prohibitive and inconvenient.

To overcome these difficulties there was a need for the development of new drug delivery system; which can improve the therapeutic efficacy and safety of drugs by more precise spatial and temporal placement within the body thereby reducing both the size and number of doses.

Transdermal[8] drug delivery system are topicaly administered medicaments. In the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication.

Transderma[4] patches are flexible pharmaceutical preparation of varying sizes, containing, one or more active ingredients. They are intended to be applied to the

unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers.

These devices allow for pharmaceuticals to be delivered across the skin barrier. Theoretically, transdermal patches works in a very simple way. A drug is applied in a relatively high dosage to the inside of patch, which is worn on the skin for an extended period of time. Though a diffusion process, the drug enters the bloodstream directly though the skin. Since there is high concentration on the patch and low concentratin in the blood, the drug will keep diffusing into the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.

Nicotin patch was the very first transdermal patch in market of India. The first transdermal patch, scopolamine was approved in 1979.

ADVANTAGE AND DISADVANTAGE

Advantages[7]

i) They can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administration drug.

ii) They can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhea.

iii) To avoid the first pass effect e.g. Transdermal Nitroglycerin. It is rapidly metabolized by the liner when taken orally.

iv) They are noninvasive, avoiding the inconvenience of parenteral therapy.

v) They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. Tradermal clonidine 7 day.

vi) The activity of drugs having a start half life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.

vii) Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.

Disadvantages

i) Some patients[7] develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.

ii) Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's imperability.

iii) Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable.

iv) Long time adhere is difficult.

COMPONENTS OF TRANSDERMAL PATHCHES

(I) Polymer Matrix[1]

The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in transdermal patches.

(a) Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.

(b) The polymer should be stable.

(c) The polymer should be nontoxic

(d) The polymer should be easily of manufactured

(e) The polymer should be inexpensive

(f) The polymer and its deagration product must be non toxic or non-antagonistic to the host.

(g) Large amounts of the active agent are incorporated into it.

Types of polymer

(a) **Natural polymers**

Cellulose derivative, Gelatin, Waxes, Proteins, Gum, Shellac, Natural rubber, starch.

(b)**Synthetic Elastomers**

Hydrin rubber, silicone rubber, Nitrile, Acrylonitrile,Neoprene.

(b) **Synthetic polymers**

Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamiode, polyurea, epoxy.

(II) Drug

Drug solution in direct contact with release liner.

Physiochemical properties

(a) The drug should have a molecular weight less than 1000 Daltons.

(b) The drug should have affinity for both lipophilic and hydrophilic phases.

(c) The drug should have a low melting point.

Biological properties

(a) The drug should be potent with a daily dose of the order of a few mg/day.

(b) The half life ($t_{½}$) of the drug should be short.
(c) The drug must not produce allergic response.
(d) Tolerance to the drug must not develop under the near zero-order release profile of transdermal patches.

(III) Permeation Enhancer
The flux J. of drug across the skin can be write

As

$$J = D\, dc/dx$$

J = The Flux
D = diffusion coefficient
C = Concentration of the diffusing spectes
X = Spatial coordinate

(a) Solvent
These compounds increase penetration possibly by swelling the polar pathway.
e.g.: Water alcohols–Methanol & ethanol, / Dimethyl acetemide Propylene glycol and Glycerol.

(b) Surfactants
The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.
i) Anionic surfactant :- Sodium lauryl sulphate Diacetyl sulphosuccinate
ii) Nonionic Surfactant :-Pluronic F127, Pluronic F68
iii) Bile Salt:- Sodium taurocholate , Sodium deoxycholate.

(b) **Miscellaneous Chemicals**
(c) Enhance the permeation eg. Urea, calcium thioglycolate.

(IV) Other excipients
(a) Adhesives
The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device.
i) It should not be irritant
ii) It should be easily removed
iii) It should not leave an un washable residue on the skin
iv) It should have excellent contact with the skin.
v) Physical & chemical compatibility with the drug
vi) Permeation of drug should not effected.

(V) Linear [11]
Protect the patch during storage. The linear is removed prior to use.

(VI) Backing
Protect the patch from the outer environment.

Types of Transdermal Patches
There are four types of transdermal patches:

(I) Single–layer drug in–adhesive[14]
The adhesive layer of this system also contains the drug. In this type patches the adhesive layer not only serves to adhere the various layer together, along with 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.

Fig. 1: Single–layer drug in–adhesive

(II)Multi-layer drug in adhesive
The multi layer drug in adhesive is similar to the single layer system in that both adhesive layer are also responsible for the releasing of the drug. But it is different however that it adds another layer of drug in – adhesive, usually separated by a membrane. This patch also has a temporary liner – layer and a permanent backing.

Fig.2: Multi-layer drug in adhesive

(III) Drug reservoir-in-adhesive: Reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug sol^{n} or susp^{n} separated by the backing layer. In this type of system the rate of release is zero order.

Fig. 3: Drug reservoir-in-adhesive

(IV) Drug reservoir-in-adhesive

This matrix system has a drug layer of semisolid matrix containing a drug sol^{n} or susp^{n}. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

Fig.4: Drug matrix-in-adhesive

FORMULATION OF TRANSDERMAL PATCHES

(i) Membrane permeation – controlled system[1]

These system can be multilaminate process e.g. Transdermal Nitro. These products consist of three substrates held together by two layers of drug containing adhesive. First the drug is processed into the physical / chemical form required for incorporation into the product. Then the drug adhesive components and excipients are mixed with a solvent to achieve uniform solution.These adhesive composition are deposited as a thin film on moving substances rate which are subsequently dried to remove solvent.

Then lamination of the dried adhesive film and other layer to form the five layer product consisting of release linear contact adhesive control membrane, drug reservoir and backing substrate. The lamination then printed and die cut into final dosage form. The production are then packed in individual foil pouches. After inspection the products are automatically inserted into a continuously moving web of pouch stock which is sealed around the dosage form.

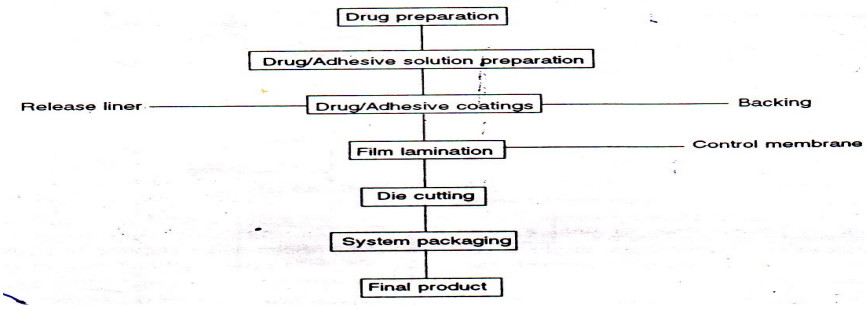

Fig.5: Multilaminate transdermal dosage from manufacturing process flow diagram

(2) Adhesive dispersion type system

The manufacturing process these systems can be divided into following parts.

(I) Preparation of individual matrix solution

Raw material [Polymer, tackifier, saftening agent] is dissolved in an organic solvent to obtain a standard or stock sol^{n}. The matrix solution then prepared from the stock solution by mixing it with ingredients specified by the formulation. The active ingradient and other non-soluble additives are added.

(II) Coating the individual matrix layers

The individual layers are made by coating the solution (above). On the smooth paper or film web and removing the solvent by drying using coating machine.

This machine consists of two units **(A) the coating unit (B) drying unit.**

(a) Coating unit

The solvent based formulations are coated onto the appropriate web. Depending on the viscosity, solid contents, flow ability and surface tension of the matrix solution.

(b) Drying Unit

Closed to the environment and is directly connected to the drying unit to avoid solvent and this active agent evaporation. The solvent is evaporated from the adhesive mars by running the coated web through a drying channel using a transport system like cranked shaft, conveyor belt.

(I) **Building the multilayer laminate**

Lamination is used to build up the multilayer matrix system. Here two matrix layers, each adhering to one side of the web are laminated., Then a carrier material of this two layer laminate is removed and a third layer, with the laminated side to the laminated side of the two layer laminate is pressed. This procedure is repeated until the final laminate is complete.

(II) **Separating unit of the multilayer laminate**

The bulk product is slit longitudinally and the individual unit is punched quit from the narrow rolls so obtained. Precision of the operations is of paramount importance here hence it affects the release rate of the active ingredient. Then the liner is applied with the necessary release aids to the system.

(III) **Packaging**

Primary packaging is done using sealed, four cornered while secondary packaging in cardboard boxes precedes shipment.

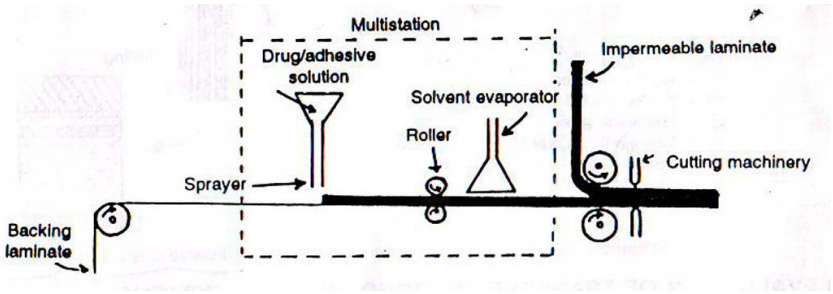

Fig. 6: The process and equipment involved in the manufacture of an adhesive dispersion system

(III) Matrix diffusion controlled system

The drug is dispersed in an insoluble matrix of rigid non swellable hydrophobic material. Materials used for rigid matrix are insoluble plastics such as PVC and fatty and materials like stearic and beewax.

With the plastic materials the drug is generally kneaded with the solution of Polyvinyl chloride in an organic solvent and granulated waxy matrix is prepared by dispersing the drug in molten fat followed by congealing. The granules are then compressed into tablets swellable matrix system are popular for sustaining the release of highly water soluble drug. The material for such matrices are generally hydrophilic gums and may be of

natural origin (guar gum, tragacanth) semi synthetic (HPMC, CMC) or synthetic (poly cryamides) The drug and the gum are granulated together with a solvent such as alcohol and compressed into tablets. The release of drug from such initially dehydrated hydro gels involves simultaneous absorption of water and desorption of drug via a swelling controlled diffusion mechanism. The gum swells and the drug diffuse out of it the swallen mars devoid of drug appears transport.

(IV) **Microsealed dissolution–Controlled system or Encapsulation[12]**

The drug particles are coated or encapsulated by one of the several micro encapsulation techniques with slowly dissolving materials like cellulose, PEGs, polymethacrylates, waxes. The resulting pellets may be filled as such in hard gelatin capsule. The dissolution role of coat depends upon the solubility and thickness of the coating which may range from 1 to 200 microns.

CHARACTERIZATION OF TRANSDERMAL PATCHES

(A) Physical evaluation

(i) Drug content uniformity[16]

It is determined by taking specific no. of patches and completely dissolving then in specific media. Resulting solution is filtered out through membrane filter. The samples so obtained is analyzed by HPLC or U.V. spectrophotometer.

(ii) Determination of surface pH

Specific number of patches are kept in contact with distilled water and excess water is drained and pH noted by pH meter.

(iii) Holding endurance[16]

It is calculated by cutting the patch in specific size by using sharp blade. Folding endurance was determined by repeatedly following a small strip of the patch at the same place till it broke. The no. of time the patch could be folded at the same place without breaking gave the value of folding endurance.

(iv)Thickness of patches

The thickness of transdermal patches is measured using micrometer screw gauge.

(iv) Weight of patches

Specific number of patches of each formulation are weighed individually in digital balance and calculated standard deviation.

(v) Moisture content[17]

The prepared patches are cut into strips of specific size. The strips are then weighed individually and kept in a dessicator containing activated silica at 30^0C for 12 hours. The films are reweighed individually until a constant weight is obtained.

Percentage (%) of moisture content = Loss in wt./ Initial wt. x 100

(vi) Water absorption studies

Transdermal films are into strips of specific size. A strip is weighed and kept in a dessicator at 40^0 C for 24 hours, removed and exposed to 75% RH (Containing saturated solution of sodium chloride) at room temperature weight is taken until a constant weight is obtained.

Water absorption capacity = Increase in weight / Initial weight x 100

(vii) Drug carrier Interaction[16]

Thin layer chromatography (TLC) or HLPC method is used for the drug carrier interaction studies.

(viii) Tack properties[1]

Tack is the ability of a polymer to adhere to a substrate with little contact pressure. It is depends on the molecular weight and composition of polymer.Test of tack includes.

(a) Thumb tack test[1]

This is a subjective test in which evaluation is done by pressing the thumb briefly into the adhesive.

(b) Rolling ball tack test[1]

This test involves measurement of the distance that a stainless steel ball travels along an upward – facing adhesive. The less tacky the adhesive the for they will travel.

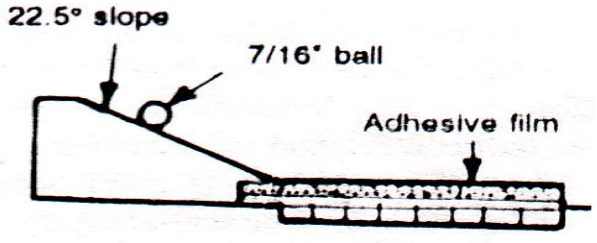

Fig. 7: Rolling ball tack test for adhesive evaluation

(b) Quick stick (Peel-tack) test[1]

The Peel force required to break the bond between on adhesive and substrate is measured by pulling the force away from the substrate at 90° at a speed of 12inch / min

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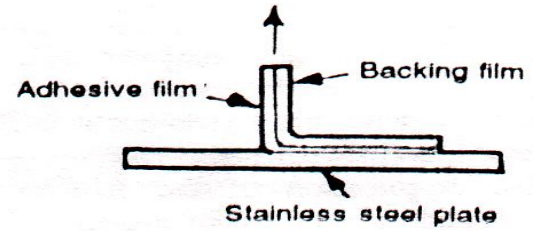

Fig. 8: Quick stick test for adhesive evaluation

(c)Probe tack test[1]

The force required to pull a probe away from on adhesive at a fixed rate is recorded at tack.

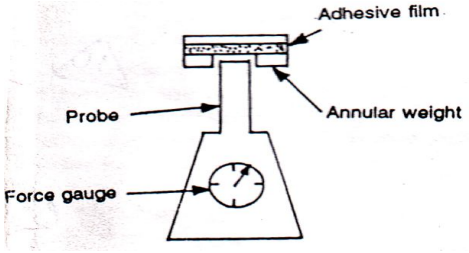

Fig. 9: Probe tack test for adhesive evaluation

(IX)Peel adhesion properties[1]

Peel adhesion is the force required to remove an adhesive coating from a test substance. It is tested by measuring the force required to pull a single coated tape, applied to a substance at 180° angle. It should not damage the skin and no residue on the skin.

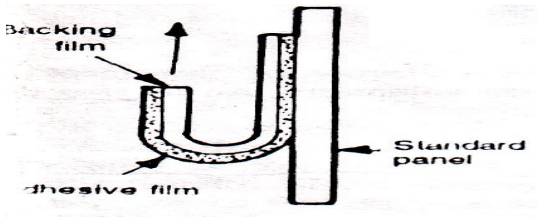

Fig. 10: Peel adhesion test for adhesive evaluation

(X)Shear strength properties [1]

Shear strength is the measurement of the cohesive strength of an adhesive polymer. Adequate cohesive strength of a device will mean that the device will not slip on application and will leave no residue on removal. It is determined by measuring the time it takes to pull on adhesive coated tape off a stainless steel plate when a specified weight is hung from the tape which pulls the tape in a direction parallel to the plate.

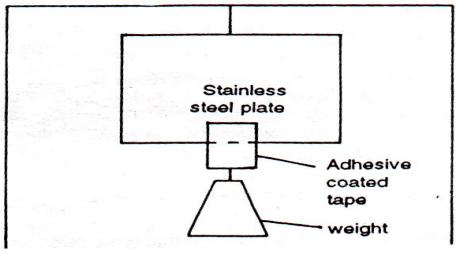

Fig. 11: Shear strength test for adhesive evaluation

(XI)Tensile strength[1]

The mechanical properties are determined using plastic tensile test performed using an instron instrument.

(B)Invitro method[1]

These are valuable techniques for screening and for measuring fluxes. Partition coefficients and diffusion coefficients because the investigator can closely control laboratory conditions.

(i)In-*vitro* permeation studies

K-C cell (Keshary –chein) diffusion cell is used if skin of rats are used. Hairless skin is used and skin is thoroughly cleaned of any adhering tissues or blood vessels and equilibrated for an hour in pH 7 buffer before running for experiment. The K.C. cell or skin piece was mounted between the compartment of the diffusion cell and donor compartment and epidermal part of skin upward or toward donor compartment. The patch to be tested was placed on skin. Specific butter media at 37^0 C $\pm$ 1^0 C is used as receptor phase and stirred with magnetic stirrer. Specific amount of sample withdrawn at regular period through the sampling port and fresh receptor fluid was added. Absorbance of sample is measured spectrophotometrically at against blank. The cumulative amount of drug permeated is ploted against

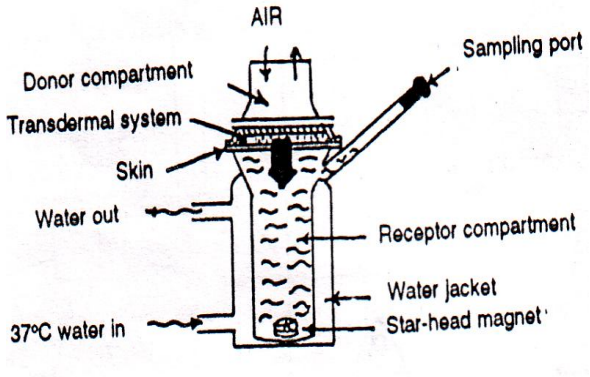

Fig. 12: K.C. Method of In-*vitro* permeation studies

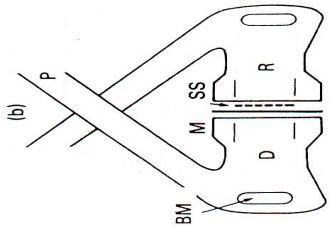

Fig. 13: Simple[11] Glass Diffusion Cell Suitable for Human Skin

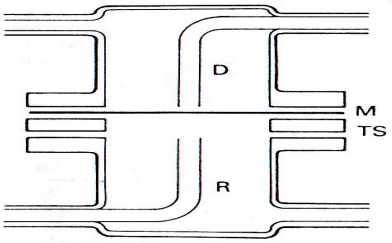

Fig. 14: Glass[11] Cell with Continously Circutliating Donor and Receptor Solution

D = Donor Compartment; R =receptor compartment; M =membrane; TS= Teflon Support

(i) In-*vitro* drug release studies[15]

A modified dissolution apparatus consisting of a jacketed vertical glass beaker 18cm long and 48cm in diameter was used for assessment of the release of drug from patches. The specific amount of formulation of buffer solution. The patch to be evaluated is struck on to the depression (15mm internal diameter and 1.5mm depth) on a teflon block fabricated for the purpose and is put into the glass beaker containing the dissolution medium. The apparatus was equilibrated to 37 + 2^0 C and operated at 50 rpm.

Specific amount of sample pipette out of reguler interval of time. Sample are filtered out through filter paper and finally membrane filtered the sample is analyzed by the HPLC or U.V. spectrophotometer.

(B)In-*Vivo* methods[1]

In vivo evaluation of trandermal patch can be carried out using –

i) Animal models

ii) Human Volunteers

(i)Animal models

In *Vivo* animals models are preferred because considerable time and resources are required to carry out studies in humans. Some of the species are used : mouse, rat, guinea pig, rabbit, rat, cat, dog, pig, house, monkey small hairy animals (e.g. rat, rabbit) or rhesus monkey is most reliable or in vivo evaluation of transdermal patches standard radiotracer

methodology used. The application site is generally the abdomen which are the least hairy site on the animals body. The compound is applied after light clipper showing of the site.

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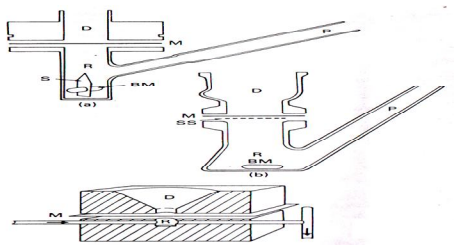

Fig.15: Diffusion[11] cells for simulation of in *vivo* conditions (not to scale).(a) Teflon and glass cell. (b) Glass cell with stainless steel support for the membrane. (c) Stainless steel cell with flow through receptor solution. D, donor compartment; R, receptor compartment; M, membrane; P, sampling port; BM, bar magnet;S, polyethylene sail;SS, stainless steel support.

ii)Human models

Human subjects should give pertinent information with minimum risk to the subjects within responsible period. It is first described by Fieldman and Maibach. They includes determination of percutaneous absorption by an indirect method of measuring radioactivity in excreta following topical application of the labeled drug. 14C is generally used for radio labeling. Determination of absorption following topical administration requires the investigator to know the amount of radioactivity retained in the body or excreted by routes. The percentage of dose absorbed transdermally is then calculated as.

$$\% \text{ Close absorbed} = \frac{\text{Total radioactivity exerted after topical Administration}}{\text{Total radioactivity exerted intervenes was Administration}}$$

The procedure takes 5-7 days for completion. Other following method.

(a)Reservoir technique

It makes use of the relationship between stratum cornium reservoir function and in vivo percutaneous absorption to predict in vivo penetration. This method is involves a simple, short exposure of the skin to the compound under study followed by removal of the stratum corneum by tape stripping and analysis of the content of the compound in the stratum corneum. For this analysis, it is possible to predict the amount of drug that will penetrate over a longer period of time.

(b)Mass balance technique

The application site is covered with an occlusive chamber, the chamber being replaced by a new one after a particular time interval. The site is also subjected to washing at these time. Radio labeling techniques are used and the chamber, washing and the faces and urine of the patients are subjected to analysis. In this technique include achievement of Mars balance between the applied close and exertion level and measurement for predicting percutaneous.

(c)Cutaneous toxicological evaluation

The major cutaneous toxicological reaction and the method are following

(I) **Contact dermatitis**

It can be either contact irritant or contact allergic

dermatitis.

(d)**Contact irritant dermatitis**

It results from direct toxic injury to cell membrane, cytoplasm or nuclei. This is generally manifested (to show, clearly especially a feeling) by inflammation and itching and can occurs from the drug, vehicle, absorption an enhancer. Contact irritant

dermatitis involves use of animals like rabbis and guinea pig. A major part of the screening deals with testing in humans. Two types of protocols are used.

a.)I **Ten day primary skin irritation test**
A panel of ten subjects has the test agent applied daily for two weeks at the site to be used in clinical situation. The test agent is left in place over the weekend between the first and second five days of repeated application, Adverse reaction consists of erythemia and scaling which are graded daily prior to the re-application of the agent on a 0 to 3 scale of none, mild, moderate and servers or a 0 to 6 scale to permit more discrimination.

a.)II Twenty one day skin irritation test
Same procedure as about is repeated but there are 25 volunteers and application is on a daily basis for 5 day a week for 21 day. The following test are the never methodologies for assessing cutaneous toxicity and are noninvasive procedure.

(a)Laser Doppler
This test is based upon the fact that as a laser light beam passes through a specimen. It is scattered when it impinges (strike or fall against) upon either static structure or moving object. Light beam scattered in static tissue will not undergo any frequency shift while those encountering moving object will. Doppler effect by illuminating the skin with a monochromatic laser light and electronically process. the frequency mix of the back scattered light collected by a photo editor system at the skin surface, a continuous measure of the red cell flux. In the micro-vascular bed can be obtained. The irritation will lead to an increase in cutaneous flow and thus increased red cell flux.

(b)Evaporative water loss measurement
Contact irritation also disturb the skin barrier and causes an excessive water loss from the damaged surface than can be measured by means of evaporimetry.

(c)Contact allergic dermatitis
Contact allergic dermatitis involves a fast immunological reaction to an antigen. The antigen is viewed to be a complex formation an externally applied compound and skin proteins. The reaction easily distinguished clinically from contact irritation types of reaction. Two protocols are employed-
(I) 25 volunteers and low grade dermatitis is included in them by application of 1- 5% Sodium lauryl sulphate to enhancer penetration and maximize any allergic potential. In first 5 day in two weeks and closed test is performed.
(II) 75-200 volunteers under occlusive patch test for 5 applications. The test agent is applied in between 24 hr. rest or 48 hr. without rest. After 7-10 day rest period, challenge is done by closed patch testing, interpretation of result. Agent show an allergenic potential may still be used by millions of patients with adverse effect.

TRANSDERMAL PATCHES IN PRESENT SCINERIO: MARKETED PRODUCTS

The market[10] for transdermal products has been in a significant upward trend that is likely to continue for the future. An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally. The table gives detail information of the different drugs which are administered by this route and the common names by which they are marketed, it also gives the conditions for which the individual system is used.

TDDS MARKETED PRODUCTS

Product Name	Drug	Manufacturer	Indication
Alora	Estradiol	TheraTech / Proctol and Gamble	Postmenstrual syndrome
Androderm	Testosterone	TheraTech / GlaxoSmithKline	Hypogonadism in males
Catapres-TTS	Clonidine	Alza / Boehinger Ingelheim	Hypertension
Climaderm	Estradiol	Ethical Holdings / Wyeth-Ayerest	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals / Berlex Labs	Postmenstrual syndrome
CombiPatch	Estradiol / Nore thindrone	Noven , Inc. / Aventis	Hormone replacement therapy
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Duragesic	Fentanyl	Alza / Janssen Pharmaceutica	Moderate / severe pain
Estraderm	Estradiol	Alza / Norvatis	Postmenstrual syndrome
Fematrix	Estrogen	Ethical Holdings / Solvay Healthcare Ltd.	Postmenstrual syndrome
FemPatch	Estradiol	Parke-Davis	Postmenstrual syndrome
Habitraol	Nicotine	Novartis	Smoking cessation
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Nicoderm	Nicotine	Alza / GlaxoSmithKline	Smoking cessation
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Nicotrol	Nicotine	Cygnus Inc. / McNeil Consumer Products, Ltd.	Smoking cessation

ADVANCE DEVELOPMENT IN TDDS

Drug[9] in adhesive technology has become the preferred system for passive transdermal delivery, two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch.

A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug molecules. These so-called "active" transdermal technologies include Ionotophoresis which uses low voltage electrical current to drive charged drugs through the skin.

- Electroporation which uses short electrical pulses of high voltage to create transient aqueous pores in the skin.
- Sonophoresis (which uses low frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (which uses heat to make the skin more permeable and to increase the energy of drug molecules).
- Even magnetic energy, coined magnetophoresis has been investigated as a means to increase drug flux across the skin.

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