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Review Article

TRANSCUTANEOUS DRUG DELIVERY SYSTEM: A COMPREHENSIVE REVIEW

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ABSTRACT

Conventional drug delivery systems are often not suitable for new protein based and other Therapeutic compounds produced by modern technology. Therefore an alternative Approach to deliver these drugs can be achieved through the skin in the form of transcutaneous drug delivery system. Modern medicine has responded with the development of methods to deliver drug transcutaneously (through) the skin for therapeutic use as an alternative to traditional route including oral, intravascular, intramuscular, subcutaneous, and sublingual. Transcutaneous drug delivery has many theoretic and practical advantage and disadvantages, and such issues are often a concern for both clinicians and patients. Transcutaneous patches are flexible pharmaceutical preparations 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. A Transcutaneous 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. Often, this promotes healing to an injured area of the body. In this method, the drug enters the bloodstream directly through skin and it avoid first pass effect. Characterization of Transcutaneous patch are necessary because check it's quality, size, time of onset & duration, adhesive property, thickness, weight of patch, moisture of content, uniformity & cutaneous toxicological studies. Their requirements for evaluation are HPLC, U.V. spectrophotometer, screw gauge, digital balance, desiccators, thin layer chromatography & K.C. Cell used.

Key words: Transcutaneous, Patch, Scopolamine Patch, Transcutaneous drug delivery, Permeation enhancer, Controlled release drug delivery.

INTRODUCTION

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has 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 is a need for the development of new drug delivery system; which will 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.[12]

Transcutaneous 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. Transcutaneous drug delivery systems are topically administered medicaments. In the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. A Transcutaneous drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier. In theory, Transcutaneous patches work very simply. 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 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. Nicotin patch first in market of India. The first Transcutaneous patch, scopolamine was approved in 1979.[13]

History of Transcutaneous drug delivery system

By now, transcutaneous drug delivery has gone mainstream and Several companies are established and dedicated to advance transcutaneous controlled release technologies. Although polymer matrix bandage formulations for typical delivery of antibiotics have been known since at least as far back as the 1950s, it is about 25 years since. Alza's first controlled release transcutaneous drug delivery system patent were issued. The Alza's patents were the first to describe the use of membranes to control the rate of drug delivery to the skin. In 1979 the first commercial transcutaneous nitroglycerine system (Alza/ciba-Geigy-Transderm Nitro QD, Key Pharmaceuticals- Nitro Dur) went on sale. Since then only a few more drugs have been found that can be delivered transcutaneously. Now, companies like powderject are developing novel mechanisms to drive drugs through the skin.[12]

Advantages

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 diarrhoea.

III.To avoid the first pass effect e.g. Transcutaneous Nitroglycerin. It is rapidly metabolized by the liner when taken orally.

IV. They are noninvasive, avoiding the inconvenience of parenteral therapy.

V. 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.

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

VII. They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. transcutaneous clonidine 7 day.[7]

Disadvantages

I.Some patients 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 transcutaneous patch because of the natural limits of drug entry imposed by the skin's impermeability.

III.Some drug e.g. transcutaneous scopolamine patch placed behind the ear, it is uncomfortable.

IV.Long time adhere is not possible.

Desirable features of a Transcutaneous drug delivery system

I. Should provide sufficient flux.

II.Must contain adequate amount of drug so that it can not become depleted before the end of desire dosage period, which is typically 1-7 days.

III.Should control the rate of delivery to avoid any overdosing resulting from normal use.

IV.Must maintain the chemical and physical stability to the patch itself to perform reliability after aging.

V.Should be non irritating to the skin in regard to chemical sensitivity, chemical irritation and mechanical irritation.[12]

Mechanism Of Transcutaneous Absorption

Structure of the skin

The skin is composed of epidermis, dermis, and underlying subdermal tissue. The epidermis and dermis are separated by a basement membrane, whereas the dermis remains continuous with the subcutaneous and adipose tissues. The epidermis is composed of five layers of cell types, beginning from the outside of the skin-stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. Within the dermis lie varying number of hair follicles and sebaceous glands along the apocrine and ecrine sweat gland, all supported by a rich vascular network. In the case of transcutaneous drug absorption the confined layer of stratum corneum, provides the rate limiting step to drug penetration. The structure of the stratum corneum has been compared to that of "bricks and mortar" 10 to 15 layers of flattened cornfield cells constitute the bricks, and lipid-rich intercellular and lipid apparatus form an effective barrier to transepidermal water loss and to external chemical access. If a drug is to pass through the skin and into the general circulation, it must first transverse this barrier.

Transcutaneous absorption

The general accepted theory is that transcutaneous absorption occurs through the intercellular lipid mortar rather than through the cellular bricks. The transcutaneous flow of compound across the stratum corneum is directly proportional to the concentration gradients and therefore can be attribute to passive diffusion. Highly lipophilic with low molecular weight demonstrates the greatest flow rate through the stratum corneum. Additionally, as the surface area exposed to a drug increases and as the thickness of the epidermis decreases, the rate of transcutaneous flux increases. Therefore the drug must maintain the affinity for both lipid and aqueous environments for effective absorption. The oil water partition coefficient of the drug-that is, its relative solubility in oil versus water- and the polarity of drug must then be considered. There are several other physiochemical properties of the drug preparation in effectiveness of the transcutaneous transport, including the drug stability or volatility, use of a solvent carrier or vehicle, use of penetration enhancer, and type of delivery device. A drug should be remaining on the skin without evaporating or becoming otherwise inactive due to spontaneous chemical breakdown. A simple method to accomplish this situation has been to suspend the drug in a vehicle-any gel, lotion, or paste used to apply the drug to the skin. Penetration enhancer included several compounds that are mixed into the vehicles to alter the molecular environment of the epidermis, most often the lipid mortar of the stratum corneum, and facilitate the drug absorption. Finally, the delivery system itself occasionally proves to be the ultimate determinate of transcutaneous drug flow.[12]

Types Of Transcutaneous Drug Delivery System

Transcutaneous delivery is an attractive route for systemic administration because of the accessibility of the skin as well as the patient acceptability. There are various types of transcutaneous therapeutic system for long term continuous infusion of therapeutic agents. Including antihypertensive, antifimgal, analgesics, steroidal and contraceptive drugs. There are following types of transcutaneous drug delivery systems

Membrane Modulated System

In this system the drug reservoir is totally encapsulated in a shallow compartment molded from a drug impermeable backing and a rate controlling polymeric membrane. The drug molecules may be released only through the rate controlling polymeric membrane. The rate limiting membrane can be a microporous or a nonporous polymeric membrane. On the external surface of membrane, a thin layer of drug compatible, hypoallergenic, adhesive polymer eg. Silicon or polyacrylate adhesives may be applied to achieve intimate contact of the transcutaneous system with the skin.

Examples of this system are

Nitroglycerine releasing -Transderm-nitro (ciba).

Scopolamine releasing -Transderm scop (ciba).

Clonidine releasing -Catapres (Boehringer Ingelheim).

Adhesive Diffusion- Controlled System

in this system the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting, onto a flat sheet of drug-impermeable backing membrane to form a thin drug reservoir layer.On the top of the drug reservoir layer, layers of non medicated, rate controlling adhesive polymer of constant thickness are applied to produce an adhesive diffusion controlled drug delivery system.

Examples of this system are-

Nitroglycerine releasing-Deponit system (Pharma-Schwartz)

Isosorbide dinaitrate releasing- Frandol tape (Toaeiyo)

Matrix-Dispersion Type System

In these systems the drug reservoir is formed by homogenously dispersing the drugs in a hydrophilic or lipophilic polymer matrix, and the medicated polymer then is molded into a medicated disc with a defined surface area and a controlled thickness. The disc is then glued onto an occlusive base plate in a compartment fabricated from a drug impermeable backing. The adhesive polymer is spread along the circumference to form a strip adhesive rim around the medicated disc.

Examples of this system are

Nitroglycerine releasing-Nitro Dur system (key)

Microreservoir System

in these systems, the drug reservoir is formed by first suspending the drug particles in an aqueous solution of water soluble polymer and then dispersing it homogenously in a lipophilic polymer by high shear mechanical force to form a large number of unleachable microscopic spheres of drug reservoirs Example is - Nitro disc system.

Components Of Transcutaneous Drug Delivery System

Polymer Matrix

The polymer controls the release of the drug from the device. Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it. The following criteria should be satisfied for a polymer to be used in transcutaneous patches.

- The polymer should be stable.
- The polymer should be nontoxic
- The polymer should be easily of manufactured
- The polymer should be inexpensive
- The polymer and its deagration product must be non toxic to the host.
- Large amounts of the active agent are incorporated into it.

Example of polymers

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

Synthetic Elastomers: Hydrin rubber, silicone rubber, Nitrile, Acrylonitrile,1Neoprene.

Synthetic polymers: Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene,

polyamiode, polyurea, Expoxy.

THE DRUG: Drug solution in direct contact with release liner.

Physiochemical properties

- The drug should have a molecular weight less than 1000 Daltons.
- The drug should have affinity for both lipophilic and hydrophilic phases.
- The drug should have a low melting point.

Biological properties

- The drug should be potent with a daily dose of the order of a few mg/day.
- The half life ($t_{1/2}$) of the drug should be short.
- The drug must not produce allergic response.
- Tolerance to the drug must not develop under the near zero-order release profile of transcutaneous patches.

Permeation Enhancer: The flux J. of drug across the skin can be written as

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

J = The Flux

D = diffusion coefficient

C = Concentration of the diffusing species

X = Spatial coordinate

Solvent: These compounds increase penetration possibly by swelling the polar pathway.

Example:-Water alcohols–Methanol & ethanol, / Dimethyl acetemide Propylene glycol and Glycerol.

Surfactants: The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

- Anionic surfactant :- Sodium lauryl sulphate, Diactyl sulphosuccinate
- Nonionic Surfactant:-Pluronic F127, Pluronic F68, etc.
- Bile Salt:-Sodium taurocholate, Sodium deoxycholate, sodium tauroglycocholate.

Miscellaneous Chemicals: Enhance the permeation eg. Urea, calcium thioglyconate.

Other Excipients

Adhesives: The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally. Both adhesive system should fulfill the following criteria.

- It should be non irritate to skin or cause an imbalance in the normal skin flora during its contact time with the skin.
- It should be easily removed.
- It should not leave an unwashable residue on the skin.
- It should have excellent contact with the skin.
- It should be physical & chemical compatibility with the drug.
- Permeation of drug should not effect.

Linear: Protect the patch during storage. The linear is removed prior to use.

Backing membrane: Protect the patch from the outer environment and prevent drug from leaving the dosage form through the top e.g. metallic plastic laminate plastic backing with absorbent pad and occlusive base plate etc.[10]

Formulation Of Transcutaneous Drug Delievery System

Membrane Permeation Controlled System

These systems can be multilaminate products e.g. Transcutaneous-Nitro and Estraderm. 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 compositions 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 farm. The production is 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 farm. Then individual pouches are cut from the web & shingled on a conveyor, packed into cartons or blisters and stored for shipment.[7]

Principal of Reservoir (or Membrane) Devices

These devices are used when drug permeation is rapid and absorption should therefore be controlled by controlling drug release (R1< R2). It is also suitable for potent drugs with low therapeutic indices where monitoring drug levels in a narrow range is essential. The drug is usually contained within the reservoir as a suspension in a liquid (such as a silicone) or gel carrier.

Rate controlling factors

- Membrane thickness
- Membrane permeability
- The rate controlling thin polymeric membrane is made of olefin polymers and copolymers, cellulosic esters, polyamides or PVC. When applied on skin, the device show a rapid release at first (initial burst effect) followed by a constant zero order release as long as the solution inside the reservoir is saturated.[10]

Adhesive Dispersion Type System

The manufacturing process these systems can be divided into

Preparation of individual matrix solution

Raw material [Polymer, testifier, saftening agent] is dissolved in an organic

solvent to obtain a standard or stock sol[8]. The matrix solution then prepared from the stock solution by mixing it with ingredients specified by the formulation. The active ingredient and other non-soluble additives are added.

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

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.

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.

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.

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 sence it affects the release rate of the active ingredient. Then the liner is applied with the necessary release aids to the system.

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

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 beeswax. 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 far 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, tregacanth) semi synthetic (HPMC,CMC) or synthetic (poly-acryamides) 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 swollen mars devoid of drug appear transport. [10]

Principle OF Monolithic (or Matrix) devices

These devices are used when R2 is the rate controlling step (R2 < R1) and the drug has larger therapeutic index so that overdosing does not precipitate toxic reaction. The two categories of matrix devices are one which the drug is dissolved (usually below saturation levels) in the polymer matrix and the other in which the drug is dispersed (generally much above saturation levels). The polymers employed for matrix system may be hydrophilic or lipophilic and includes PVC, PVP, polysaccharides, polyester, microporous, and polypropylene and ethylene vinyl acetate copolymers.

Rate controlling factors

- Drug concentration in polymer matrix
- Chemical nature of polymer matrix
- Geometry of device
- The drug release rate from matrix system is rapid initially and falls as the matrix get depleted of drug. The rate is thus proportional to the square root of time. [7]

Microsealed Dissolution Controlled System Or Encapsulation: 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.

Evaluation of transcutaneous drug delivery system

Physical evaluation

Drug content uniformity: 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 are analyzed by HPLC or U.V. spectrophotometer.

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.

Holding endurance: 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.

Thickness of patches: The thickness of transcutaneous patches is measured using micrometer screw gauge.

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

Moisture content: The prepared patches are cut into strips of specific size. The strips are then weighed individually and kept in a desiccators containing activated silica at 30°C far 12 hours. The films are reweighed individually until a constant weight is obtained.

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

Water absorption studies: Transcutaneous films are into strips of specific size. A strip is weighed and kept in a desiccator at 40° C far 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

Drug carrier Interaction: Thins layer chromatography (TLC) or HLPC method is used for the drug carrier interaction studies.

Tack properties: 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.

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

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

Quick stick (Peel – tack) test: 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.

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

Peel adhesion properties: 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.

Shear strength properties: 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.

Tensile strength: The mechanical properties are determined using plastic tensile test performed using an instron instrument. [10]

***In-vitro* method:** These are valuable techniques for screening and for measuring fluxes. Partition coefficients and diffusion coefficients because the Investigator can closely control laboratory conditions.

***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° C ± 1° 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.

***In vitro* drug release studies:** 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 Teflon block fabricated for the purpose and is put into the glass beaker containing the dissolution medium. The apparatus was equilibrated to 37 + 2° C and operated at 50 rpm. Specific amount of sample pipette out of regular 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.

***In-Vivo* methods:** In vivo evaluation of transcutaneous patch can be carried out using –

- Animal models
- Human Volunteers

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, pairteis rat, cat, dog, pig, house, monkey small hairy animals (e.g. rat, rabbit) or rhesus monkey is most reliable or in vivo evaluation of Transcutaneous patches standard radiotracer methodology used. The application site is generally the abdomen which is the least hairy site on the animal's body. The compound is applied after light clipper showing of the site.

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 include 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 transcutaneously is then calculated as.

$$\% \text{ Close absorbed} = \frac{\text{Total radioactivity exerted after topical Administration} \times 100}{\text{Total radioactivity exerted intervenes was Administration}}$$

To overcome the limitation inherent in the method described above, various refinements have been made. These are describing below:

Reservoir technique: It makes use of the relationship between stratum corneum 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. Far this analysis, it is possible to predict the amount of drug that will penetrate over a longer period of time.

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 times. 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 far predicting percutaneous.

Cutaneous toxicological evaluation: The major cutaneous toxicological reaction and the method are following

Contact dermatitis: It can be either contact irritant or contact allergic
dermatitis.

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

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 erythema 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.

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.

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.

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

Contact allergic dermatitis: Contact allergic dermatitis involves a hast immunological Rxn to an antigen. The antigen is viewed to be a complex formation an externally applied compound and skin proteins. The Rxn easily distinguished clinically from contact irritation types of Rxn. Two protocols are employee.

- 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.
- 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.

Growth of microorganism

Localized superficial infection: Bacteria, yeast, and fungi may proliferate under occlusive dressings due to favorable factor like increased temperature, hydration, pH etc. The potential of any system for promoting growth of microorganism can be evaluated by quantitative bacteriological cultures of skin sites before and after use of transcutaneous system using non ionic detergent. Cultures can be taken before and after repeated application e. g. before and after a 10 or 21 day irritation study. These results can be topically extended to give a reasonable estimate of the potential growth of pathogens such as S. aureus and G. albicans.

Miliaria: Miliaria (prickly heat) can develop under a occlusive dressings when there is a strong thermal stimulus for sweating. Resident bacteria may proliferate under an occlusive dressing and produce toxins which damage sweat duct epithelium. A PAS positive necrotic coagulum of damaged sweat duct epithelium develops which interferes with the delivery of sweat to skin surface by sweat duct obstruction. So, a strong thermal stimulus for sweating leads to rupture of sweat duct epithelium and consequent inflammation due to extravasated sweat. The usual clinical reaction is that of a discrete pruritic inflammatory papule (Miliaria rubra). This reaction is not a problem when the period of application of the system is short. However, prolonged application will lead to greater prevalence of this reaction.[10]

Marketed Product Of Transcutaneous Drug Delivery System

The highest selling transcutaneous patch in the United States was the nicotine patch which releases nicotine to help with cessation of tobacco smoking. The first commercially available vapour patch to reduce smoking was approved in Europe in 2007. The patches

release essential oils that help the smoker to reduce gradually the number of cigarettes instead of stopping the smoking abruptly.

Nitroglycerin

Nitroglycerin transcutaneous drug delivery system used in treatment of angina. The physicochemical and pharmacokinetic properties of nitroglycerin, solubility and apparent partition coefficient, extensive first pass metabolism and are very good for transcutaneous drug delivery. The dose does required to maintain required therapeutic blood levels (µg/ml) for 24 hrs is about 10 mg and it is very easy to deliver it in less than 50 cm" patch. Transcutaneous drug delivery system of over a decade and substantial progress has been used achieved over the years. Therapeutic effect is usually with an hour of application of transcutaneous drug delivery system and persists for about 30 mins. after removal of patch.

The preference to a particular transcutaneous drug delivery system is based on comfort, anaesthetics and adhesiveness. Transcutaneous drug delivery systems are applied on hair free area and the site of administration should be in rotation. In one study using nitro.dur transcutaneous drug delivery system, the pharmacokinetics/pharmacodynamics was studied in healthy volunteers. The plasma levels were achieved in about an hour and showed significant haemodynamic effects. The effects include increase in heart rate and decrease in end diastolic dimension due to dilation of peripheral venous vessels. Prophylactic use of transcutaneous drug delivery system of nitroglycerin in angina has resulted in about 63% decrease in the frequency of angina attacks at rest. Resting blood pressure was reduced, whereas there was no effect on exercise-induced increase blood pressure, but exercise-induced angina pectoris was less severe and shorter in duration.

All clinical studies indicated transcutaneous drug delivery system on nitroglycerin are effective in patients with angina and have shown significant increase in patient compliance. Although the dosage regimen of nitroglycerin results in constant blood levels of nitroglycerin metabolites.[10]

Scopolamine

Transcutaneous scopolamine was the first transcutaneous system approved in the U.S. with liable specifications of rate-controlled delivery. It is indicated for the prevention of motion sickness. The Transcutaneous system is contained in a thin disk that the patient places on intact skin, usually behind the ear. The unit has multiple layers including a backing membrane, a drug reservoir consisting of solid drug suspended in a liquid vehicle, a microporous rate-controlling membrane a skin contact adhesive. Scopolamine is a well- known antiemetic drug; however, it causes undesirable side effects when given in conventional tablets. These side effects appeared to be related to the wide fluctuations in scopolamine concentration in blood that occur between doses. The Transcutaneous scopolamine system is applied only once every 3 days and provides relatively constant blood levels of scopolamine over this period.

The Transcutaneous product delivers 0.5-mg scopolamine over 3 days. A priming quantity of 140µg of drug is released at asymptomatically declining rate over 6 hrs., stabilizing at a maintenance rate of 5 µg/hr for the remainder of the 3-days period. The Transcutaneous product delivers 0.5 mg scopolamine over 3 days. A priming quantity of 140 µg of drugs is released at an asymptomatically declining rate over 6 hrs, stabilizing at a maintenance rate of 5µg/hr for the remainder of the 3 days period. Efficacy of transcutaneous scopolamine has been compared with oral dimenhydrinate and placebo. The Transcutaneous device was applied 13.5 to 15 hr before exposure to motion, and again 2.5 hr after motion began. In the study, directly comparing transcutaneous scopolamine with oral dimenhydrinate, the transcutaneous medication protected 79% of the subjects from motion sickness, whereas the oral drug protected 58%; in a second study, protection rates of 68% and 41% were found for the scopolamine and dimenhydrinate therapy, respectively. No patient was protected by the placebo .e.g. Transderm Scop System (CIBA)

Transcutaneous Present & Future Aspect

Present trends

Today a number of transcutaneous patches for drugs exist. Patches have been useful in enabling new therapies and in reducing first pass effect for example transcutaneous estradiol patches are use by over a million patients per years, in contrast to oral formulations, are not associated with liver damage. Transcutaneous clonidine, nitroglycerin & fentanyl patches exhibit fewer adverse effects than conventional oral dosage forms. Of particular note has been the value of nicotine patches in preventing smoking & prolonging life. For example, 2 years after being on Transcutaneous patches for 12 weeks, 4 times as many patches wearers did not smoke compare to patients who received placebos.

Commercial successes can be found in following therapeutic categories[1]

I. Smoking cessation
II. Asthma
III. Pain management
IV. Cardiovascular disease
V. Woman's health
VI. Neutraceuticals

FUTURE DEVELOPMENTS

Future development of transcutaneous drug delivery systems will likely focus on the increased control of therapeutic regimens and the continuing expansion of drugs available for use transcutaneous drug delivery system have been considered for use in the development of antihistamines, antarthritics, antiaddictives, beta blockers, antiemetic, calcium channel antagonist, tranquilizers, antiasthmatics, antiretroviral agent, hormones and centrally acting cholinergic agents. Alternative transcutaneous drug delivery system may entail the use of methods such as iontophoresis or phonophoresis. Iontophoresis is the application of an electric current to the skin to facilitate the movement of chemicals through the epidermis. Iontophoresis serves to enhance the absorption of large polar molecules and peptide such as insulin. Phonophoresis uses ultrasonic irradiation to increase transcutaneous drug absorption. Its effectiveness has not yet been proved conclusively, but further investigations are in progress.

The number of drugs formulated in 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. One reason for this undoubtedly is the fact that only certain specialized firms can manufacture transcutaneous patches. Companies prefer to have full control of their projects, and to enjoy the higher profits on products developed and manufactured in house. Another reason is that only a limited number of drugs fit the molecular weight, lipophilicity, and potency requirements for transcutaneous adsorption.[12]

CONCLUSION

The relatively noninvasive nature of transcutaneous drug delivery, and the fact that this route can simultaneously avoid problems associated with presystemic metabolism and mimic (at least, to some extant) parental input profiles, are significant advantages. Conventional drug delivery systems are often not suitable for new protein based and other therapeutic compounds produced by modern technology. Therefore, an alternative approach to deliver these drugs can be achieved through the skin in the form of transcutaneos drug delivery system, which release the drug at a predetermined rate over at extended period of time. Various approaches for the development of transcutaneous drug delivery system are used like membrane modulated, adhesive diffusion controlled system, matrix dispersion type and microreservoir system Basic components are used in

transcutaneous drug delivery system are polymer matrix or matrices, the drug permeation enhancers, other excipients. Absorption via the transcutaneous route primarily occurs by passive diffusion through the stratum corneum. The rate of diffusion is dependent on the permeability coefficient of the drug, the applied concentration of the drug, the surface area of the skin exposed to the drug and the thickness of the epidermis (Fick's low of diffusion) Transcutaneous drug delivery systems are formulated by commonly film casting method. Transcutaneous drug delivery systems are stabilize by performing various stability tests as per WHO and ICH guidelines. Transcutaneous drug delivery systems are evaluated by various official and non official tests as per pharmacopoeias and other resources. Novel Transcutaneous drug delivery systems are iontophoresis, Electroporation, Sonophoresis, Microporation, Needles jet injectors. Heat as a means of increasing skin permeation. Marketed products of transcutaneous drug delivery system are - Scopolamine, Nitroglycerin, Clonidine, Nicotine, Estradiol.

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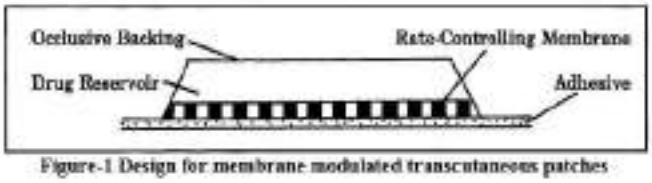


Figure-1 Design for membrane modulated transcutaneous patches

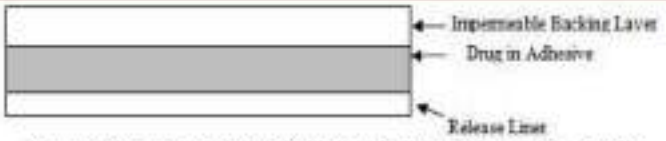


Figure-2 Design for adhesive diffusion controlled transcutaneous patch

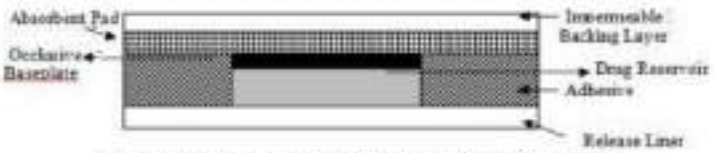


Figure-3 Design for matrix dispersion transcutaneous patch

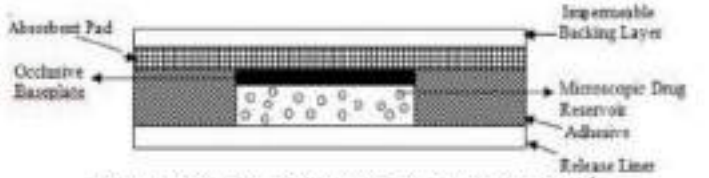


Figure-4 Design for microreservoir transcutaneous patch [1]

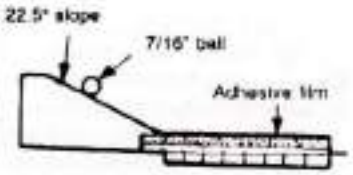


Figure-5 Rolling ball tack test for adhesive evaluation

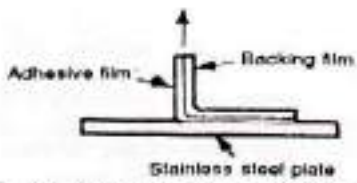


Figure-6 Quick stick test for adhesive evaluation

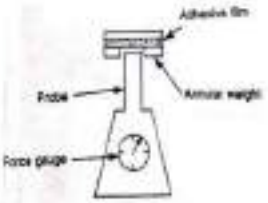


Figure-7 Probe tack test for adhesive evaluation

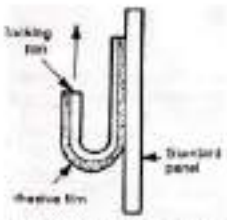


Figure-8 Peel adhesion test for adhesive evaluation

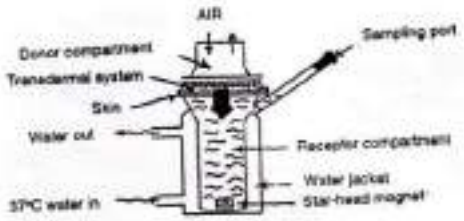


Figure-9 :K.C. Method of In vitro permeation studies