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A Review On Trasdermal Drug Delivery System

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ABSTRACT

Release of drugs via the skin has been always a challenging part for research due to obstacle properties shown by the outermost layer of skin stratum corneum. In the previous two decades, the transdermal drug delivery system has turn into a established technology that offers important clinical repayment over additional dosage forms. Because transdermal drug delivery offers controlled as well as programmed rate of release of the drug into the patient, it is capable to maintain steady state blood concentration. It's a advantageous form of drug delivery because of the apparent advantages e.g. suitable and pain-free self-administration for patients, prevention of hepatic first-pass metabolism and the GI tract for poorly bioavailable drugs than other routes of deliverance.Thepresent article reviews the choice of drug candidates and polymers, advantages, disadvantages of formulation, design and the methods of evaluation, augmentation techniques based on drug/vehicle optimization such as selection of drug, prodrugs and ion pairs, supersaturated drug solutions, vesicles, liposomes, particles and complexations. This review also emphases on the recent innovations in TDDS, which be able to used for the research and improvement of pharmaceutical dosage form intended for transdermal drug delivery.

Keywords: Transdermal drug delivery system, first pass metabolism, site specific, Iontophoresis.

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INTRODUCTION

Transdermal drug delivery system (TDDS) provides a sustain drug release as well as lessen the amount of action and thus decrease the side effects related with its oral therapy. The principal of transdermal drug transportation is to distribute drug across epidermis to accomplish systemic effect over a extended period of time. Now days, the transdermal route has turn into one of the most successful method for research in pharmaceutical sciences. Transdermal drug delivery systems (TDDS) dosage forms planned to deliver a therapeutically active drug through the skin.[1]The morphological, biophysical and physicochemical properties of the skin be supposed to be measured in order to deliver therapeutic active agents via the human skin. [2]

A number of significant advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, augmented therapeutic efficiency and continuation of steady plasma level of the drug.

The basic components of any transdermal delivery system consist of the drug(s) dissolved or dispersed in a reservoir or inert polymer matrix; an outer backing film of paper, plastic, or foil, and a pressure-sensitive adhesive that anchors the patch to the skin. The adhesive is covered by a release liner which needs to be peeled off before applying the patch to the skin.

The first Transdermal system, Transderm-SCOP was accepted by FDA in 1979 for the avoidance of nausea and vomiting related with travel, particularly by sea. The different drugs which can be administered via skin patches consist of scopolamine, nicotine, estrogen, nitroglycerin, and lidocaine.

Transdermal delivery not only provides controlled, constant administration of the drug, but also allows constant input of drugs with short biological half-lives, and eliminates pulsed access into systemic circulation and therefore prevents unwanted side effects.

Advantages: [3,4,5,6,7]

1. Transdermal medication provides safe, convenient and pain-free self-administration for patients.
2. Transdermal delivery may be helpful in those patients who are polymedicated.
3. Transdermal drug delivery provide a constant rate of release of drug to sustain absorption of drug for a longer period of time as to evade peak and valley related with oral dose and parenteral administration.
4. Transdermal patches enhances therapeutic effects of different drugs by avoiding problems associated with drugs such as pre-systemic metabolism, low absorption, gasto intestinal annoyance etc.

5. Helpful for drugs who possesses short half-life as to prevent frequent administration.
6. Reduced inter & intra-patient variability by simplified prescription schedule.
7. Greater improvement in those patients who are unconscious, dysphagia or constipation.
8. Elimination of pre-systemic metabolism result in decline the quantity of drug administered, results in the reduction of adverse effects and therefore safer in hepato-compromised patients.
9. The drug release can be terminated at any time by removing transdermal system.
10. Transdermal systems are usually inexpensive and economic.
11. Enhanced therapeutic effectiveness.

Disadvantages: [8,9,10]

1. Limited skin permeability.
2. constrained to potent drug.
3. Unsuitable for large molecule (>500 Dalton).
4. Significant lag time.
5. Difficulty for adhesion.
6. The drug which shows degradation in the skin.
7. Variation in absorption efficiency a different sites of skin.
8. Many drugs especially drugs with hydrophilic structures permeate the skin too slowly to be of therapeutic benefit.
9. Only small, lipophilic drugs can be delivered through the skin.
10. Skin irritation and hypersensitivity reactions might happen.

Important properties of TDDS:[9]

Table 1: Important properties of TDDS.

Properties	Comments
Shelf life	Up to 2 years
Patch size	< 40 cm^2
Dosing frequency	Once a day to once a week
Appearance	Clear, tan or white color
Packaging	Easy removal of release liner and minimum steps requisite for application
Skin reaction	Non irritating and non-sensitizing
Release	steady pharmacokinetic and pharmacodynamic profiles
Dose	low
Half life (h)	10 or less
Molecular weight	< 400
Skin reaction	Non irritating and non sensitizer

Oral bioavailability	Low
Therapeutic index	Low

Structure and composition of skin:[8]

The skin is largest organs of the human body having an area of about $2m^2$ of human adult. Human skin comprises of three different but mutually dependent tissues:

(A) The stratified, vascular, cellular epidermis.

(B) Underlying dermis of connective tissues.

(C) Subcutaneous layer or hypodermis.

Every layer has its own function and importance for maintaining the integrity of skin and thus the body structure. [1]

Epidermis: [4]

The multilayered epidermis varies in thickness, depending on size and number of layers, ranging from 0.8 mm on palms and 0.06 mm on the eyelids. Stratum corneum and the rest of the epidermis, also known as viable epidermis, cover a major area of skin.

Stratum corneum: [4]

This is the outermost layer of skin, about 10 mm thick. It is flexible but quite impermeable. The stratum corneum is the major barrier for penetration.

Viable epidermis: [4]

This is located under the stratum corneum and varies in thickness starting 0.06 mm on the eyelids to 0.8 mm on the palms. Going inwards, it consists of different layers as stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale.

Dermis: [5]

Dermis is about 3 to 5 mm thick layer and is mainly composed of a matrix of connective tissue which contains blood vessels, lymph vessels, and nerves. It also provides nutrients and oxygen to the skin at the same time as removing toxins and waste products.

Hypodermis: [5]

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. This layer helps to control temperature, provide dietary support and mechanic defense. It carries major blood vessels and nerves to skin and might contain sensory pressure organs.

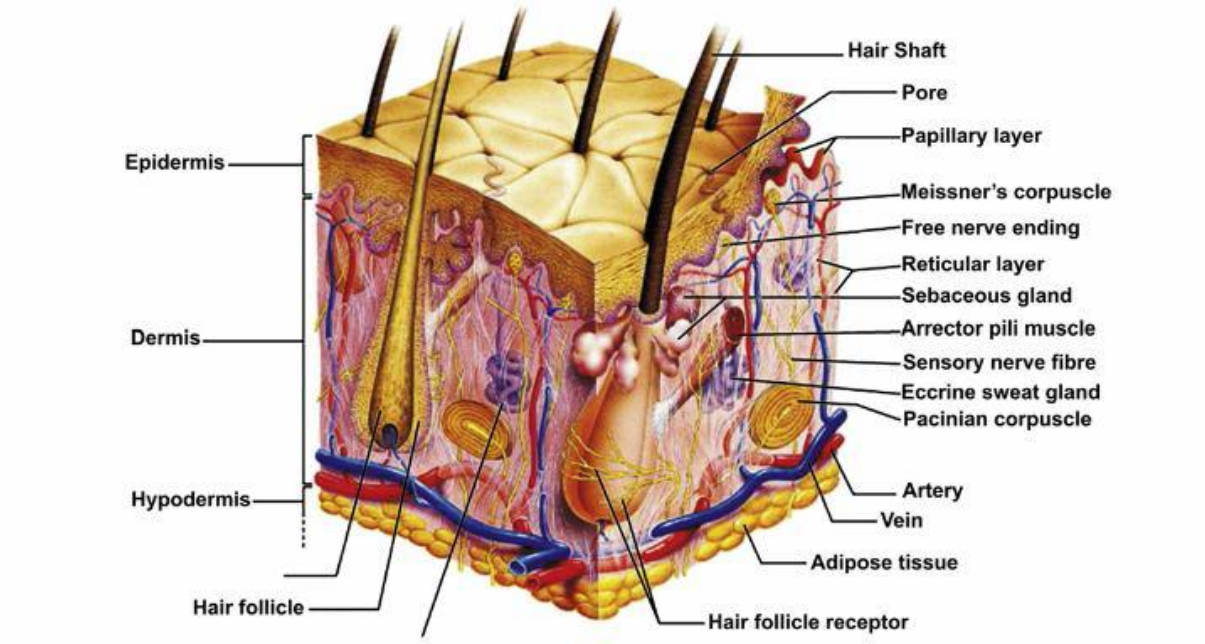

Figure 1:Structure of human skin. [4]

Mechanism of transdermal permeation: [10]

For a active drug to reach a target tissue, it have to acquire some physicochemical properties which assist the absorption of the drug from the skin and also the uptake of the drug via the capillary network within the dermal papillary layer (Figure 2).

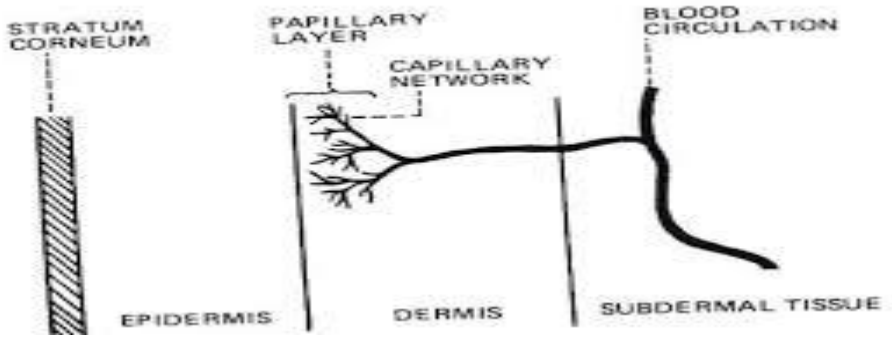

Figure 2: Simplified model of the human skin for mechanistic analysis of skin permeation.

Transport through the skin: [11,1,2,12]

Skin is structurally complex and thick covering. Molecules from the environment should penetrate the stratum corneum. They required to then enter the viable epidermis, the papillary dermis and the capillary walls into the blood stream or lymph channels, where they are removed from the skin by blood or lymph.

Route of drug penetration through human skin: [12]

When a molecule reaches skin, it contacts with cellular debris, microorganisms, sebum and other materials. The diffusant subsequent to that has three potential entry routes to the viable tissue, via

the hair follicles through their associated sebaceous glands, via the sweat ducts or across the stratum corneum connecting these appendages.

The figures demonstrate three possible routes for drug penetration

1. Intra cellular or trans cellular: across the cells.
2. Intercellular or paracellular: between the cells.
3. Transfollicular.

The main pathway for diffusion of small polar molecules is likely to be transcellular and through stratum corneum. The intercellular route is considered an doubtful route because of its volume and lengthy path length. The transfollicular passageway in which the drug movements through cells and crossways them is the shortest mode the most likely provides comparatively large area for diffusion of a molecule. The transfollicular pathway shows route or diffusion of drug molecule throughout the hair shaft openings which apparently are packed with sebum.

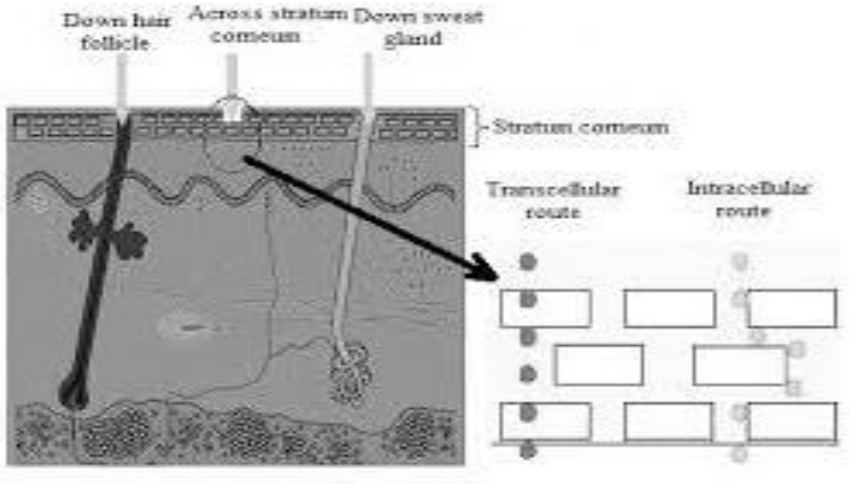

Figure 3: Simplified diagram of stratum corneum and its routes of drug penetration

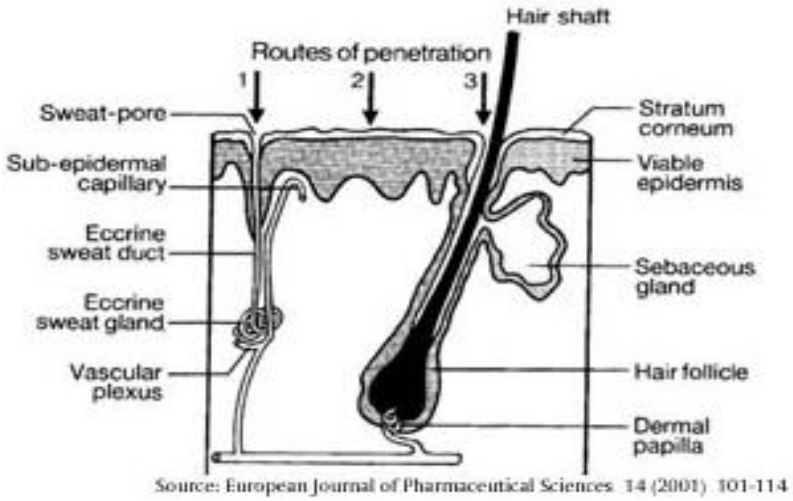

Figure 4: Pathways through human skin

Transcorneal permeation:[13]

Intra cellular permeation:

Drug particle passes from the cells of the stratum corneum. It is usually seen in case of hydrophilic drugs. while stratum corneum hydrates, water accumulates near exterior of the protein filaments.

Intercellular permeation:

Non-polar substances pursue by mean of intercellular penetration. These molecules dissolve within and distribute through the non- aqueous lipid matrix imbibed among the protein filaments.

Transappendegeal permeation:[14]

In this path, the drug molecule could transverse through the hair follicles, the sebaceous passageway of the pilosebaceous apparatus or the aqueous path of the salty sweat glands though this route may be of some significance for large polar compounds. The transdermal penetration can be visualized as combination of a series in sequence as:

1. Adsorption of a penetrant particle on the surface layers of stratum corneum.
2. Diffusion via stratum corneum and through viable epidermis.
3. lastly throughout the papillary dermis into the microcirculation.

Factors affecting transdermal bioavailability:[14]

Two main factors affect the bioavailability of the drug through transdermal routes:

Physicochemical factors:

Skin hydration:

In contact through water the permeability of skinincreases appreciably. So use of humectant is done this system.

Temperature and pH:

The penetration of drug augments ten folds withtemperature difference. The diffusion coefficientdecreases as temperature decreases. Weak acids and weak bases dissociate depending on the pH andpKa or pKb value.Temperature and pH are essential factorsaffecting drug diffusion.

Diffusion coefficient:

Permeation of drug depends on diffusioncoefficient of drug. At a constant temperature,the diffusion coefficient of drug molecule depends onproperties of drug, diffusion medium andinteraction among them.

Drug concentration:

The flux is proportional to the concentrationgradient across the barrier, concentrationgradient is high if the concentration ofdrug is more across the barrier.The optimal partition coefficient (K) is necessary for good action.

Molecular size and shape:

Drug absorption is inversely related tomolecular weight, small molecules go throughfaster than big ones.

Biological factors:[13]

Skin state:

Diseased condition of patient alters theskin conditions. The intact skin is better barrierbut disease affectpenetration ability of skin.

Skin metabolism:

Skin shows metabolism of steroids, hormones, chemicalcarcinogens and some drugs. So skin metabolismdetermines efficiency of drug permeated fromthe skin.

Skin age:

The young skin is more permeable than elder.Children are more sensitive for skin absorption of toxins. Therefore, age is one of the factoraffecting penetration of drug in TDDS.

Basic components of TDDS: [15,16,17]

1. Polymer matrix/Drug reservoir.
2. Drug.
3. Permeation Enhancers.
4. Pressure sensitive adhesives.
5. Backing Laminate.
6. Release Liner.
7. Other excipients.

POLYMER MATRIX/DRUG RESERVOIR

Polymers are important component of TDDS, which control the release of the drug from the system. Polymer matrix can be made by dispersion of drug in liquid or solid state synthetic polymer base. The polymers used for TDDS can be classified as,

Natural Polymers:

Cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.

Synthetic Elastomers:

Polybutadiene, hydrin rubber, polyisobutylene, siliconrubber, nitrile, acrylonitrile, neoprene, butylrubber etc.

Synthetic Polymers:

Polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc.

Drug:

The best drug candidates for passive adhesive transdermal patches should be non ionic, of low molecular weight, contain adequate solubility in oil and water, a low melting point and should be potent.

The following are a number of of the desirable properties of a drug for transdermal delivery:

(a) Physiochemical Properties:

1. The drug should comprise of molecular weight less than about 500 Daltons.

2. The drug should posses affinity for both lipophilic and hydrophilic phases. The drug must have a low melting point.

(b) Biological Properties:[17]

1. The drug should be potent.

2. The half life (t1/2) of the drug should be small.

3. The drug should not cause a cutaneous or allergic response.

4. Drug which degrade in the G.I tract or shows first pass effect are suitable candidates for transdermal delivery.

Permeation Enhancers:

Three pathways are recommended for drug penetration throughout the skin: polar, nonpolar,and polar/non-polar. The enhancers act by changing one of these pathways. The key to altering the polar pathway is to do protein conformational change or solvent swelling. Enhancers can enhance the drug diffusivity in the Stratum Corneum by dissolving the skin lipids or by means of denaturing skin proteins.

Chemical Enhancers:

These agents act through increasing the drug permeability from the skin by causing reversible damage to the SC or by enhancing thermodynamic activity of the drug by functioning as co solvent or by increasing the partition coefficient of the drug to promote its discharge from the vehicle into the skin or by conditioning the SC to encourage drug diffusion.

Eg: Sulphoxides, Azone, Pyrrolidones, Fatty acids.

Pressure sensitive adhesives:

A PSA is a material that helps in maintaining a close contact between transdermal system and the skin surface. It should adhere with low applied finger pressure, be aggressively and permanently tachy, and exert a strong holding force. Polyacrylates, polyisobutylene and silicon based adhesives are extensively used in TDDSs.

Backing Laminate: [18]

While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipient compatibility is supposed to also be considered. Some backing materials are vinyl, polyethylene and polyester films.

Release Liner: [19,20]

During storage time the patch is covered by a protective liner that is detached immediately prior to the application of the patch to skin. Typically, release liner is composed of a base layer which can be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer composed of silicon or teflon.

Other excipients:

A variety of solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to offer plasticity to the transdermal patch.

Approaches to develop transdermal therapeutic systems: [21,22,23]

A number of technologies have been effectively developed to provide a rate control over the release and the transdermal penetration of drugs. These technologies can be classified into two main categories as follows:

A. Rate-programmed transdermal DDS.

B .Physical stimuli-activated transdermal DDS.

A. Rate-programmed transdermal DDS:

1. Membrane permeation – controlled systems.
2. Adhesive dispersion – type systems.
3. Matrix diffusion – controlled systems.
4. Micro reservoir type or micro sealed dissolution controlled systems.

B. Physical stimuli-activated transdermal DDS:

i. Based on Structure based: microneedles ,macroflux .

ii Electrical driven: Iontophoresis, Ultrasound,Photochemical waves, Electroporation, Electroosmosis.

iii. Based on velocity: Powder jet, Needle free injection.

iv. Miscellaneous: Transferosomes , Heat, Laser radiation ,Magnetophoresis.

Membrane penetration-systems:[23]

In this kind of system, drug reservoir is encapsulated in a superficial compartment moulded from a drug-impermeable metallic plastic laminate in addition to a rate controlling polymeric membrane that can be micro porous or non-porous. The drug molecules are allowed to release merely from

the rate controlling polymeric membrane. Inside the drug reservoir compartment, the drug solids are either dispersed homogenously in a solid polymer matrix (e.g. Polyisobutylene adhesive) or suspended in an unbleachable, sticky liquid medium (e.g. Silicon fluids) to form a paste similar to suspension.

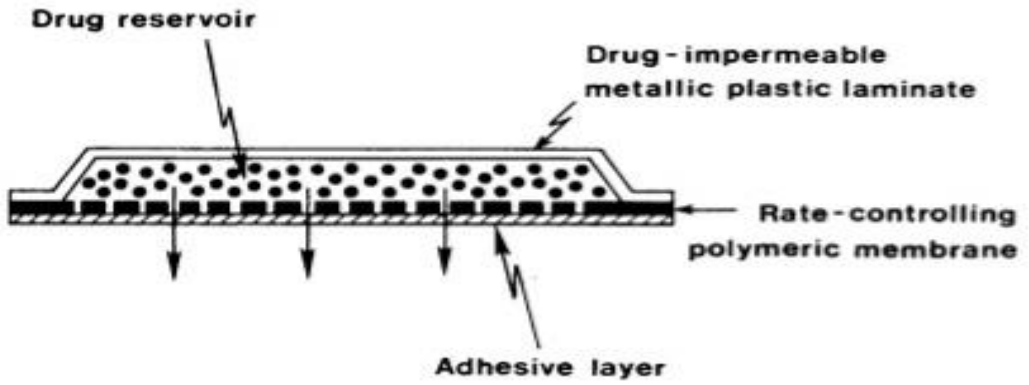

Figure 5: Membrane-moderated Transdermal drug delivery system.

The stable release rate of the drug is the most important advantage of membrane permeation controlled system.

1. Single-layer Drug-in-Adhesive:[22]

A Single-layer Drug-in-Adhesive system is characterized through the addition of the drugdirectly inside the skin-contacting adhesive. In this transdermal system, theadhesive not only serves to fix the system to the skin, but also as the formulation base, containing the drug and all the excipients in a single backing film. The release rate of drug from this type of system is dependent on the distribution across the skin. The intrinsic rate of drug release from this form of drug delivery system is defined by

$dQ/dT = Cr/1/Pm + 1/Pa$

Where Cr is the drug concentration within the reservoir compartment and Pa and Pm are the permeability coefficients of the adhesive layer and the rate controlling membrane, Pm is the addition of permeability coefficients simultaneous penetrations across the pores and the polymeric material.

2. Multi-layer Drug-in-Adhesive:[21]

The Multi-layer Drug-in-Adhesive is similar to the Single-layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive. However, the multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive or the addition of multiple drug-in-adhesive layers under a single backing film. The rate of drug release in this system is defined by,

$dQ/dt = Ka/r.\ Da\ Cr/ha$

Where Ka/r is the partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer.

Adhesive Dispersion-Type Systems:[23]

Adhesive Dispersion-Type System is a basic form of the membrane penetration controlled system. As shows in Figure-6, the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer e.g. Poly (isobutylene) or poly (acrylate) adhesive and after that distributing the medicated adhesive, by solvent casting or hot melt, on top of a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir sheet. On the top of the drug reservoir layer, thin layers of non-medicated, rate-controlling adhesive polymer of a precise permeability and even thickness are applied.

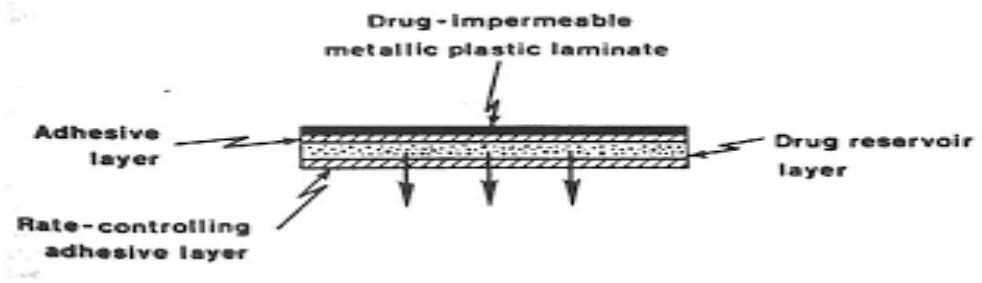

Figure 6: adhesive diffusion-controlled Transdermal drug delivery system.

The Reservoir transdermal system is characterized by means of the addition of a liquid compartment containing a drug solution or suspension separated from the release liner through a semi-permeable membrane and adhesive. The adhesive component of the product accountable for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric arrangement around the membrane. The rate of drug release from this drug reservoir controlled system can be expressed by,

$dQ/dt = Ka/r.\ Da\ A\ (\ ha\ )/ha\ (\ t\ )$

In the above equation, the thickness of the adhesive layer meant for drug molecules to distribute through increases through time ha (t). To balance for this time dependent increase in the diffusional path due to the depletion of drug dose by release, the drug loading capacity also increased with the thickness of diffusional path A (ha).

Matrix diffusion controlled systems:[22]

In this system the drug reservoir is produced by homogenously dispersing the drug moleculesinto a hydrophilic or lipophylic polymer matrix. The resulting medicated polymer is subsequently molded into a medicated disc with a distinct surface area and controlled width. The dispersion of drug particles in the polymer matrix can be obtain by either homogenously mixing the finely

ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of polymer chains or homogenously blending drug molecules through a rubbery polymer at an high temperature. The drug reservoir can be shaped by dissolving the drug and the polymer in a general solvent followed by solvent evaporation in a mould at an high temperature and/or vacuum. This drug reservoir containing polymer disc is then applied onto an occlusive base plate within a compartment fabricated from a drug impermeable plastic backing membrane. The polymer is spread by the side of the circumference of the patch to make an adhesive rim around the medicated disc. e.g. Nitro-Dur; Delivers nitroglycerin intended for the treatment of angina pectoris.

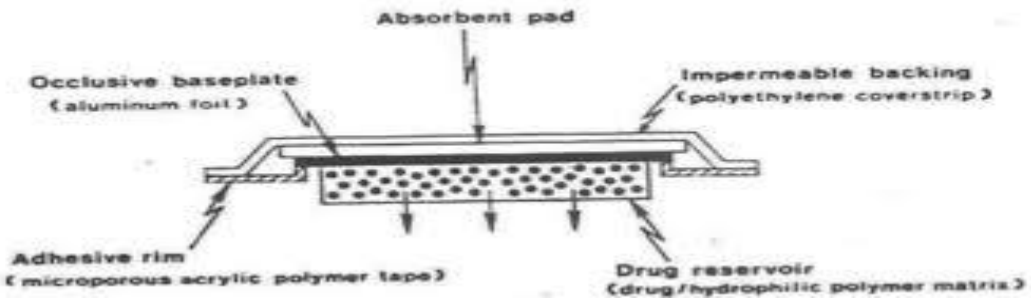

Figure.7: Matrix dispersion-type transdermal drug delivery system.

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix. The rate of drug release from this type of system is defined as,

$dQ/dt = \sqrt{(ACpDp/2t)}$ Where A is the initial drug loading dose dispersed in the polymer matrix and Cp and Dp are the solubility and diffusivity of the drug in the polymer respectively. Since, only the drug species dissolved in the polymer can release, Cp is essentially equal to CR, where CR is the drug concentration in the reservoir compartment.

Micro reservoir type or Micro sealed:[22]

The micro reservoir type drug delivery system can be considered a combination of the reservoir and matrix diffusion type drug delivery systems. In this approach, the drug reservoir is formed by first suspending the drug solids in the aqueous solution of water soluble liquid polymer (e.g. Polyethylene glycol) and then dispersing the drug suspension homogenously in lipophillic polymer viz. silicone elastomers by high energy dispersion technique to form several discrete, unleachable micro spheres of drug reservoirs. This thermodynamically unstable dispersion is quickly stabilized by immediately cross-linking the polymer chains in-situ, which produces a medicated polymer disc

with a constant surface area and a fixed thickness. A transdermal therapeutic system is then produced by positioning the medicated disc at the center and surrounding it with an adhesive rim. E.g. Nitroglycerin: Releasing TDDS for once-a-day treatment of angina pectoris.

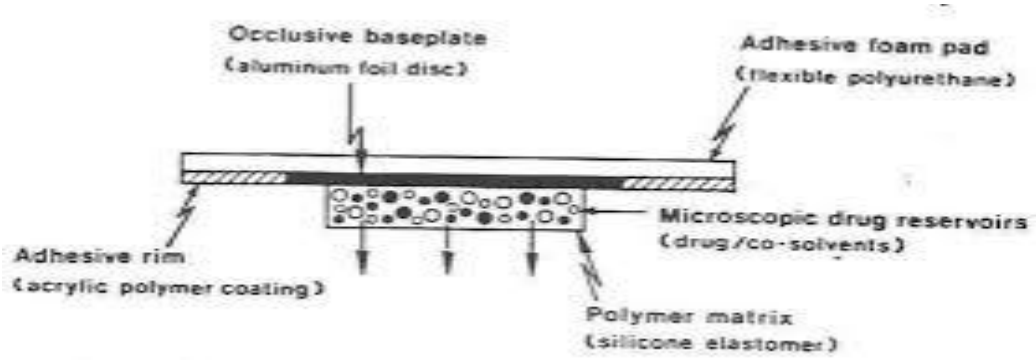

Figure 8: Micro reservoir-type transdermal drug delivery system.

The microreservoir system has been found to follow the zero order release devoid ofdanger of dose dumping. The release rate of drugs from the microreservoir system is expressed by

$$dQ/dt = DpDd\ m\ Kp/Dphd+Ddhpmkp(n\ Sp\ DI\ SI(I-n)/h1(1/k1+1/km)$$

Where

m=a/b

a is ratio of the drug concentration in the bulk elution medium above drug solubility in thesame medium.

b is the ratio of the drug concentration at the outer edge of the polymer coating above the drug solubility in the same polymer composition.

n =the ratio of drug concentration at the inner edge of the interfacial barrier over drug solubility in the polymer matrix.

DI ,Dp and Dd are correspondingly the drug diffusivities in the liquid layer surrounding the drug molecules, polymer coating member contiguous the polymer matrix and the hydrodynamic diffusion layer surrounding the polymer coating through respective thickness of h1, hp and hd

K1=the partition coefficient for the interfacial partitioning of the drug from the liquid compartment to the polymer matrix.

Km= the partition coefficient used for the interfacial partitioning of the drug from the polymer matrix to the polymer coating membrane.

Kp=the partition coefficient for the interfacial partitioning of the drug from the polymer coating membrane to the elution solution (or skin).

S1=the solubility of the drug molecules in the liquid compartment.

Sp=the solubility of the drug molecules in the polymer matrix.

Electrically-Based Techniques:[24]

Iontophoresis:

Iontophoresis can be defined as the facilitation of ionizable drug penetration across the skin by means of an applied electrical potential, the driving force of which may be merely visualized as electrostatic repulsion. A typical iontophoresis tool consists of a battery, micro-processor controller, drug reservoir and electrodes. The system involves the application of a minute electric current (usually 0.5 mA/ cm2) to a drug reservoir on the skin, by means of the correspondingly charged electrodes (on the surface of the skin) placed collectively in the drug reservoir producing a repulsion effect that efficiently drives the solute molecules away from the electrode and into the skin.

Designed for delivery of macromolecules, proteins and peptides like calcitonin, corticotrophin releasing hormone, δ-sleep- inducing peptide, dextrin sulphate, inulin, gonadotropin releasing hormone, growth hormone releasing factor, parathyroid hormone and vasopressin iontophoresis may as well be utilized.

Ultrasound:

Ultrasound (sonophoresis, phonophoresis and ultraphonophoresis) is a system for enhancing the skin penetration of drugs by means of ultrasound (20 KHZ to 16 MHZ) as a physical force. Application of low – frequency ultrasound (20 -100 KHZ) enhances skin permeability more efficiently than high frequency ultrasound (1 -16 MHZ). The method of transdermal skin penetration involves disruption of the stratum corneum lipids, consequently allowing the drug to pass throughout the skin.

Electroporation:

This technique involves the application of high voltage pulses to the skin, which has been recommended to induce construction of transient pores. High voltages in the type of direct current [DC (100 volts)] caused by electrical pulses with short treatment period (milliseconds) are most often employed. Other parameters that influence delivery include pulse properties for eg wave form, rate and number. The mechanism of permeation is the construction of transient pores due to electric pulses that consequently allow the passage of macromolecules from the outside of the cell to the intracellular space through a combination of potential processes such as diffusion and local electrophoresis.

Trandermal patches available in market: [25,26]

Table 2: Trandermal patches available in market.

Brand name	Drug	Manufacturer	Indication
Alora	Estradiol	Thera tech/Protocoland Gamble	Postmenstrualsyndrome
Androderm	Testosterone	Theratech/GlaxoSmithKline	Hypogonadism in males
Catapress	Clonidine	Alza/BoehingerIngelheim	Hypertension
Climaderm	Estradiol	Ethicalholding/Wyeth-Ayerest	Postmenstrualsyndrome
Climra	Estradiol	3M PharmaceuticalLabs	Postmenstrualsyndrome
Deponit	Nitroglycerine	Schwarz-pharma	Angina Pectoris
Duragesic	Fentanyl	Alza/JanssenPharmaceutica	Moderate/severePain
Estraderm	Estradiol	Alza/Novertis	PostmenstrualSyndrome
Fematrix	Estrogen	Ethical Holding	PostmenstrualSyndrome
FemPatch	Estradiol	Parke Davis	PostmenstrualSyndrome
Minitran	Nitroglycerine	3M Pharmaceutical	Angina Pectoris
Nicoderm	Nicotine	Alza/GlaxoSmithkline	Smoking cessation
Nitro-dur	Nitroglycerine	Key Pharmaceutical	Angina Pectoris
Nuvelle TS	Estrogen/Progesterone	Ethical Holding/Schering	Angina PectorisHormone
Testoderm	Testosterone	Alza	Hypogonadism inmales
Nitrodisc	Nitroglycerine	RobertsPharmaceutical	Angina Pectoris
Habitraol	Nicotine	Novartis	Smoking Cessation

Evaluation parameters: [27]

The evaluation parameters for transdermal delivery system can be classified into following types: Physicochemical evaluation, In vitro evaluation and In vivo evaluation;

1) Physicochemical evaluation:

Interaction studies: [27]

The drug and the excipients should be compatible with each other to produce a product that is stable. Interaction studies are done by Thermal analysis, Fourier transform infrared spectroscopy (FTIR), ultra violet and chromatographic techniques by comparing their physicochemical properties such as assay, melting point, wave numbers, and absorption maxima.

Thickness of the patch: [28]

The thickness of the transdermal patch is calculated by using a digital micrometer at different position of patch and this determines the mean thickness and standard deviation for the same to make sure the thickness of the prepared patch.

Weight uniformity: [29]

The transdermal patches are to be dried at 60°C for 4 h prior to testing. A specified area of patch is cut in different parts of the patch and weighed in digital balance. The average weight and standard deviation values are to be considered from the entity weights.

Folding endurance: [30,31]

A definite area of strip is cut and continually folded at the same place till it broke. The number of

times the film possibly will be folded devoid of breaking gave the value of folding endurance.

Percentage moisture content: [32]

The patches are to be weighed separately and to be kept in a desiccator containing fused calcium chloride at room temperature. After 24 h, the films are reweighed and the percentage moisture content calculated by below formula :

Percentage moisture content (%) = [Initial weight – Final weight / Final weight] ×100.

Percentage moisture uptake: [33]

The patches are weighed individually and kept in a desiccator containing saturated solution of potassium chloride in order to retain 84% Rhesus factor (RH). After 24 h, the films are to be reweighed and the percentage moisture uptake calculated by the formula:

Percentage moisture uptake (%) = (Final weight – Initial weight / initial weight) × 100.

Drug content: [34]

A specific area of patch is to be dissolved in a appropriate solvent in specific volume. Then, the solution is to be filtered from a filter medium and the drug content analyzed with the help of suitable method. Then, the mean of three different samples is taken.

Content uniformity test: [35]

Ten (10) patches were chosen and content calculated for individual patches. If 9 out of 10 patches possess content between 85 to 115% of the particular value and one has content not less than 75 to 125% of the particular value, then transdermal system pass the test of content uniformity. But if 3 patches posses content in the range of 75 to 125%, then additional 20 patches are tested for drug content. If these 20 patches posses range from 85 to 115%, then the system pass the test.

Flatness test: [36]

3 longitudinal strips were cut from every film at different part like one from the center, other one from the left side, and a new one from the right side. The length of each strip was calculated, and the difference in length due to non-uniformity in flatness was calculated by determining percentage restriction, with 0% constriction equivalent to 100% flatness. Constriction (%) = I1 - I2 × 100 I1

Where, I1 = initial length of each strip. I2 = final length of each strip.

Shear Adhesion test: [35]

This test is done for determination of the cohesive strength of an adhesive polymer. An adhesive coated tape is applied on top of a stainless steel plate; a specified weight is hung from the tape, to influence it pulling in a direction parallel to the plate. Shear adhesion strength is calculated by

measuring the time it takes to pull the tape from the plate. The longer the time get for removal, greater is the shear strength.

Peel Adhesion test: [33]

In this check, the force requisite to remove an adhesive coating form a test substrate is known to as peel adhesion. A single tape is applied to a stainless steel plate or a backing membrane of preference and then tape is pulled from the substrate at a 180º angle, and the force necessary for tape detached is taken.

Thumb tack test: [36]

It is a qualitative examination useful for tack property determination of adhesive. The thumb is merely pressed on the adhesive and the relative tack property is determined.

Flatness test: [37]

Three longitudinal strips are to be cut from each film at different part like one from the center, other one from the left side, and a new one from the right side. The length of each strip was considered and the variation in length was calculated.

Rolling ball tack test:[35]

This test determines the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls downward and comes into get in touch with horizontal, upward facing adhesive. The distance the ball travels by the side of the adhesive provides the measurement of tack, which is expressed in inch.

Quick Stick (peel-tack) test: [32]

In this analysis, the tape is pulled away from the substrate at 90ºC at a rate of 12 inches/min. The peel strength requisite to break the bond between adhesive and substrate is calculated and recorded as tack value, which is shown in ounces or grams per inch width.

Probe Tack test: [34]

In this test, the tip of a clean probe by a defined surface roughness is brought into make contact with adhesive, and when a bond is formed among probe and adhesive. The consequent removal of the probe mechanically breaks it. The force necessary to pull the probe away from the adhesive at predetermined rate is recorded as tack and it is expressed in grams.

Stability studies:[36]

Stability studies were conducted according to the International Conference on Harmonization (ICH) guidelines by storing the TDDS samples at 40 ± 0.5°C and 75 ± 5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyzed properly for the drug content.

2) IN VITRO evaluation of TDDS:

In vitro drug release studies:[37]

The paddle over disc method (USP apparatus V) can be used for measurement of the release of the drug from the prepared patches. Dry films of known thickness were cut into distinct shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500 ml of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was maintained at 32 ± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5 ml aliquots) can be taken at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC.

In vitro skin permeation studies: [37,38]

An in vitro penetration study can be calculated by means of diffusion cell on thick abdominal skin of male Wistar rats weighing 200 to 250 g. Hair from the abdominal region is detached carefully by using an electric clipper; the dermal side of the skin was systematically cleaned with distilled Water. Equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 prior to starting the experiment. The temperature of the cell was maintained at 32 ± 0.5°C. Sample of specific volume was taken and analyzed.

IN VIVO evaluation:[38]

Skin irritation study:

Skin irritation and sensitization determination can be done on healthy rabbits. The dorsal surface (50 cm^2) of the rabbit is to be washed and the hair removed. The patch is to be detached after 24 hr and the skin observed and classified into different grades on the base of the severity of skin damage.

CONCLUSION

The TDDS review articles give significant information about the transdermal drug delivery systems and its evaluation procedure details. Both hydrophobic and hydrophilic actives can be used for the TDDS, therefore it is one of the promising drug delivery system. To optimize this drug delivery system, superior understanding of the different mechanisms of biological interactions, and polymer are necessary to optimize this drug delivery system. TDDS a practical application as the next generation of drug delivery system. Transdermal method is effective for the inclusion of the drug to the site of action without rupturing the skin. This article gives valuable information regarding the formulation and evaluation aspects of transdermal drug delivery systems. So TDDS is a extremely promising field which is essential to be explored in the future with most research study.

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