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REVIEW ARTICLE

AN EXHAUSTIVE DETAIL OFTRANSDERMAL DRUG DELIVERY

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Abstract:
Transdermal drug delivery (TDD) is known to offer many advantages over the oral and injectable routes for systemic drug delivery. However, the skin is a complex and dynamic organ with marked barrier function, which results in limitations and variations in the amount and nature of drugs that can be delivered across the skin and into the bloodstream. Thus a continual search for ways to optimize the permeation of drugs across the skin exists, in an attempt to enhance delivery and improve patient compliance. Various type of transdermal patches are used that delivered the specific dose of medication directly into the blood stream. The review article covers a brief outline of the transdermal drug delivery system, advantage over conventional drug delivery system, influential factors in site-to-site TDDs variation, function and layers of the skin,fundamentals of skin permeation, fundamentals of skin permeation, approaches used in the development of transdermal drug delivery system, enhancement techniques, evaluation parameters of nanoparticle loaded patch.

Keywords:

Introduction

INTRODUCTION

Transdermal drug delivery systems (TDDS), also known as patches, are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism espectively1.

Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc.emerged. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug.

ADVANTAGES

- Improved patient compliance and painless simple application.
- No interference with gastric juice and intestinal fluids.
- Increase the therapeutic value of many drugs via avoiding specific problems associated with the drug like GI irritation, lower absorption, decomposition due to hepatic first pass effect.
- The route is suitable for the administration of drugs having very short half life, narrow therapeutic window and poor oral availability.
- Avoidance of first pass metabolism of drug.
- Self administration is possible in these system.
- The simplified medication regimen lead to improved patient compliance and reduced the side effects, inter and intra-patient variability.
- Transdermal medication delivers a steady infusion of a drug over a prolonged period of time. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided.
- Maintains stable or constant and controlled blood levels for longer period of time.

DISADVANTAGE

- Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.
- Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
- The delivery system cannot be used for drugs requiring high blood levels.
- The use of transdermal delivery may be uneconomic. For better understanding of transdermal drug delivery, the structure of skin should be briefly discussed along with penetration through skin and permeation pathways.
- The drug has large molecule size makes absorption difficulty. So drug molecule should ideally below 800-1000 daktons.
- Many drug with a hydrophilic structure having a low peneteration through the skin and slowly to be therapeutic benefit. Drugs with a lipophillic character, however are better suited for transdermal delivery.

INFLUENTIAL FACTORS IN SITE-TO-SITE TDDS VARIATION:

The rate and/or extent of drug penetration across the skin influences bioavailability. Mathematical models, which are designed to predict the rate and extent of absorption, have attributed the high importance of SC thickness to TDD. These models, however, make the assumption that the SC is homogenous in composition and structure, and the diffusion pathway is consistent.

Structure of skin

The skin, the heaviest single organ of the body, combines with the mucosal lining of the respiratory, digestive, and urogenital tracts to form a capsule which separates the internal body structures from external environment. For an average 70 kg human with skin surface area of 1.8 mn a typical square centimeter covers 10 hair follicles, 12 nerves, 15 sebaceous glands, 100 sweat glands, and 3 blood vessels with 92 cm total length. The skin has several functions, which can be summarized as follows.

Surface Topology

Although differences in surface characteristics, such as smoothness and the presence of hair, might be expected to influence TDB from transdermal dose forms, there are limited supportive data. Evidence suggests that differences in sebum sheet thickness between different sites may contribute to differences in the delivery of drugs to the SC. It is also reasonable to assume that soap and other topically applied preparations such as moisturizers might similarly affect TDB, as they are unlikely to be uniformly applied to all areas of the body.

Thickness

The laws describing diffusion through a membrane accord a major role to membrane thickness. In TDD, the membrane of interest is the SC, which is generally considered to be rate-limiting in transdermal permeation. Previous observations in the variations of SC thickness at different body sites have been documented with supportive measurements. Even though such variations in the SC have been used to explain the site dependence of TDD , no definite association has been established in humans or animals..

Cellular Layers and Cell Sizes

Regional variation in the number of SC cellular layers and cell sizes has also been documented. The former was thought to account for the variation in SC thickness. To date, the contribution of SC cellular layers and cell size to TDD variation remains unclear. It has been proposed that, depending on the SC thickness, the variation in cell size could lead to variation in the volume of intercellular space, which may act as the molecular ''reservoir,'' thus influencing drug penetration and absorption.

Lipid Content

The effect of delipidization in compromising the SC barrier function and alteration of solute uptake clearly implicates the involvement of the lipid pathway in the transdermal delivery of drugs. Changes in drug permeation through the skin in diseases that alter the lipid content of the skin have also substantiated the importance of lipid to drug penetration.

For instance, ichthyosis is a genetic skin disease that features hyperkeratosis, which results in the thickening and scaling of the SC due to the accumulation of cholesterolsulphate, an amphipathic lipid in the epidermis. This alteration in the lipid matrix is accompanied by a more rapid drug permeation. The lipid composition of the SC varies between the different regions of the body.

FUNCTIONS OF SKIN

- *Protection* – from invasion by microbes, chemicals, physical agents (e.g. mild trauma, UV light), and dehydration.
- *Reflex action* – due to sensory nerves to stimuli
- *3. Regulation of body temperature* – regulate body temperature about 36.8°C (98. with variation of 0.5°C to 0.75°C.4°F)
- *Formation of vitamin D* – fatty substance present in skin, 7- dehydrocholesterol, in presence of UV light from sun is converted to vitamin D.
- *Absorption* – absorbs some drug with low molecular weight as well as toxic chemicals like mercury.
- *Excretion* – excretes sodium chloride in sweat, urea when kidney function is impaired, and aromatic substances (e.g. garlic and other spices)

Anatomy and Physiology

Human skin comprises of three distinct but mutually dependent tissues.

Epidermis

The multilayered envelop of the epidermis varies in thickness, depending on cell size and number of cell layers, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum and the remainder of the epidermis so called viable epidermis cover a major area of skin.

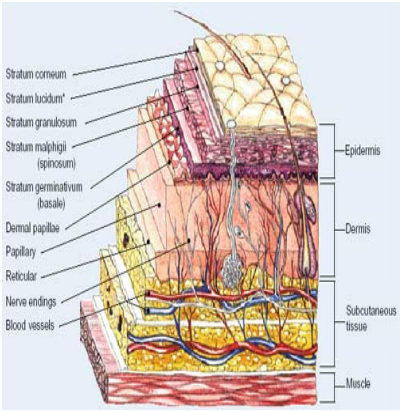


Fig: ***Structure of skin***

Stratum corneum

This is the outermost layer of skin also called as horney layer. It is approximately 10mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of parallel to the skin surface lying dead, keratinized cells, called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration.

Dermis

Dermis is 3 to 5mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels, and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin, while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of a permeate very low, and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation. The hypodermis or subcutaneous fat tissue supports the dermis and epidermis.

Hypodermis

It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanic protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery only penetration through stratum corneum is essential and then retention of drug in skin layers is desired.

FUNDAMENTALS OF SKIN PERMEATION

Until the last century the skin was supposed to be impermeable with exception to gases. However, in the current century the study indicated the permeability to lipid soluble drugs like electrolytes. Also it was recognized that various layers of skin are not equally permeable i.e. epidermis is less permeable than dermis. After a large controversy, all doubts about stratum corneum permeability was removed and using isotopic tracers, it was suggested that stratum corneum greatly hamperpremeation . A. Stratum corneum as skin permeation barrier. The average human skin contains 40-70 hair follicles and 200-250 sweat ducts per square centimeter.

Series of steps in sequence:

1. Sorption of a penetrant molecule on surface layer of stratum corneum.
2. Diffusion through it and viable epidermis, and

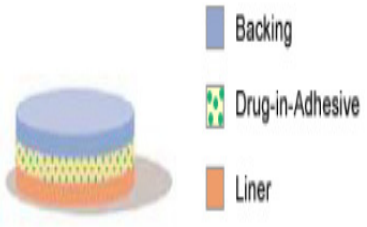
finally.

3. The molecule is taken up into the microcirculation for systemic distribution.

4. Regional variation in water permeability of stratum corneum.

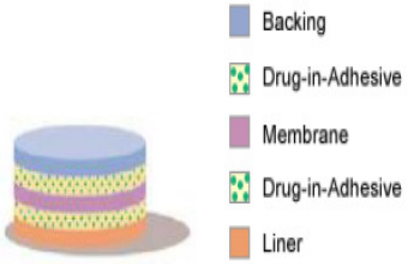
TYPES OF TRANSDERMAL PATCHES

1- Single-layer Drug-in-Adhesive-



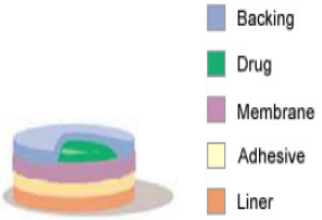
The Single-layer Drug-in-Adhesive system is characterized by the inclusion of the drug directly within the skin-contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film.

2-Multi-layer Drug-in-Adhesive



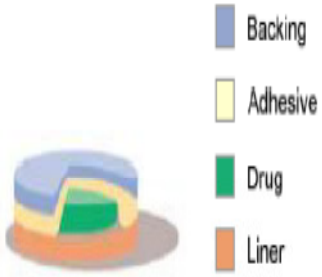
The Multi-layer Drug-in-Adhesive is similar to the Single-layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive. However, the multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive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

3. Drug Reservoir-in-Adhesive



The Reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane .

4. Drug Matrix-in-Adhesive



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.

APPROACHES USED IN THE DEVELOPMENT OF TRANSDERMAL DRUG DELIVERY SYSTEM:

1-**Membrane Permeation – Controlled Systems**

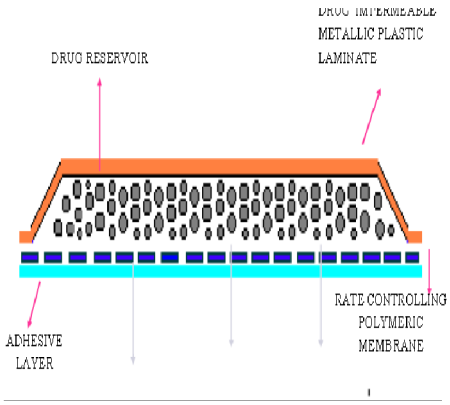
In this type of system, the drug reservoir is totally encapsulated in a shallow compartment moulded from a drug-impermeable metallic laminate and a rate controlling membrane which may be microporous or non-porous. The drug molecules are permitted to release only through the rate-controlling membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid polymer matrix or suspended in an unleachable, viscous liquid medium such as silicone fluid to form a paste like suspension.

A thin layer of drug compatible, adhesive polymer like silicone or polyacrylate adhesive may be applied to the external surface of the rate controlling membrane to achieve an intimate contact of the transdermal system and skin surface.

Examples:

- Nitroglycerin-releasing transdermal system (Transdermal-Nitro/Ciba, USA) for once a day medication in angina pectoris.
- Scopolamine-releasing transdermal system

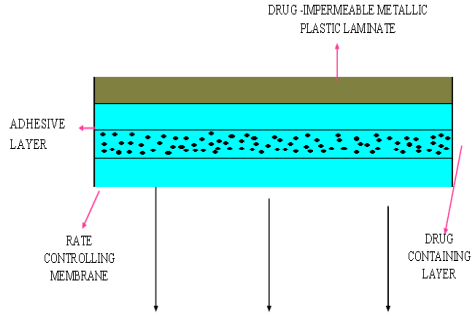
- (Transdermal-Scop/Ciba, USA) for 72 hrs prophylaxis of motion sickness.
- Clonidine-releasing transdermal system (Catapres/Boehriger Ingelheim, USA) for 7-day therapy of hypertension.
- Estradiol-releasing transdermal system (Estraderm/Ciba, USA) for treatment of menopausal syndrome for 3-4 days.



2) Adhesive Dispersion-Type Systems This system is a simplified form of the membrane permeation-controlled system. Here the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer e.g., Poly (isobutylene) or Poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer On the top of the drug reservoir layer, thin layers of non-medicated, rate controlling adhesive polymer of a specific permeability and constant thickness are applied to produce an adhesive diffusion-controlled delivery system.

Example:

- Isosorbide dinitrate-releasing transdermal therapeutic system (Frandol tape/Yamanouchi, Japan) once-a-day medication of angina pectoris .



3) Matrix Diffusion-Controlled Systems
In this approach, the drug reservoir is prepared by homogenously dispersing drug particles in a hydrophilic or lipophilic polymer matrix.
The resultant medicated polymer is then moulded into a medicated disc with a defined surface area and controlled thickness. The drug reservoir can be formed by dissolving drug and polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or vacuum. The drug reservoir containing polymer disc is then pasted onto an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing. The adhesive polymer is then spread along the circumference to form a strip of adhesive rim around the medicated disc.

Example:

- Nitroglycerin-releasing transdermal therapeutic system (Nitro-dur and Nitro-Dur II / Key Pharmaceuticals, USA).

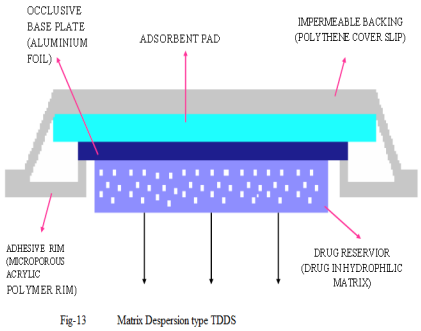


Fig-13 Matrix Despersion type TDDS

4) Microreservoir Type or Microsealed Dissolution Controlled Systems This system is a combination of the reservoir and matrix diffusion type drug delivery systems. The drug reservoir is formed by first suspending the drug solids in an aqueous solution of water-soluble liquid polymer viz. silicone elastomers by high-energy dispersion technique to form several discrete, unleachable microscopic spheres of drug reservoirs. The quick stabilization of this thermodynamically unstable dispersion is accomplished by immediately cross-linking the polymer chains *in situ*, which produces a medicated polymer disc with a constant surface area and fixed thickness. Positioning the medicated disc at the center and surrounding it with an adhesive produce a transdermal therapeutic system.

Example:

- Nitroglycerin releasing transdermal therapeutic system (Nitrodisc, Searle, USA) for once a day therapy of angina pectoris.

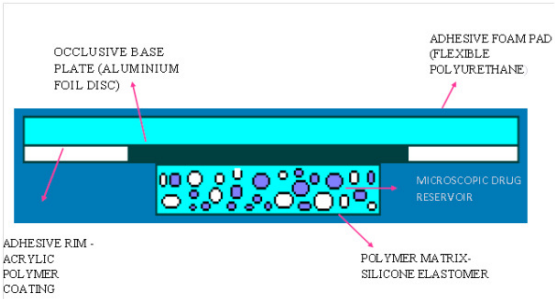


Fig- 14 Cross section of Microreservoir TDDS

TYPES OF ENHANCEMENT TECHNIQUES:

A) STRUCTURE-BASED OF ENHANCEMENT TECHNIQUES:

1. Transdermal Patches

A transdermal patch or skin adhesive patch is that device which is loaded with drug candidate and usually applied on the skin to transport a specific dose of medication across the skin and into the blood circulation. The adhesive serves two functions: It is glue in nature that keeps the patch adhered to the skin, and it acts as the suspension that holds the drug.

2. Microfabricated Microneedles

These are the devices which are having the features of both the hypodermic needle and transdermal patch that can deliver the drug that transports the drug effectively across the memberane. The systems consists of a drug reservoir and a some projections (microneedles) extending from the reservoir, these helps in penetrating the stratum cornea and epidermis to deliver the drug. Poke with patch approach- Involves piercing into the skin followed by application of the drug patch at the site of treatment.

Fabricated microniddle TDDS

Coat and poke approach- Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.

Biodegradable microneedles- Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.

3. Macroflux

These are devices having an area of around 8cm as well as 300 micro projections per cm2 with the length of individual micro projection less than 200Î¼m. Three types of Macroflux have been designed . They include, Dry-Coated Macrofluxsystem-this is used for short period delivery that consists micro projection array coated with medicament that adhered to a elastic polymer adhesive backing .

4. Metered-Dose Transdermal Spray (Mdts)

It is a liquid preparation in the form of solution that are used topically which is made up of a vehicle that is volatile come non volatile in nature, which consists the completely dissolved medicament in solution . The use of MDTS reaches the sustained level and better permeation of the drug via skin. The MDTS has the following potential advantages:

Fig: Meter dose spray

B) ELECTRICALLY-BASED ENHANCEMENT TECHNIQUES:

1. Iontophoresis

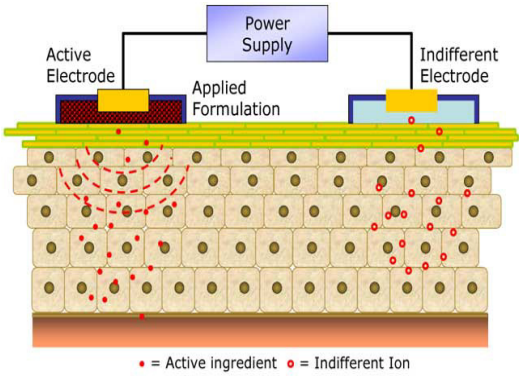


Fig: Schematic Expression of Drug Administration Facilitated By Iontophoresis.

It involves passing of current (few milliamperes) to skin limited to a certain area using the electrode remains in contact with the formulation which is to be administered. Pilocarpine delivery can be taken as example to induce sweat in the diagnosis of cystic fibrosis and Iontophoretic deliveryof lidocaine is considered to be a nice approach for rapid onset of anesthesia.

2. Ultrasound

In this technique, there is a mixing of drug substance with a coupling agent (usually with gel, cream or ointment) that causes ultrasonic energy transfer from the system to the skin. This involves rupturing the lipids present in stratum cornea, which allows the medicament to permeate via biological barrier.

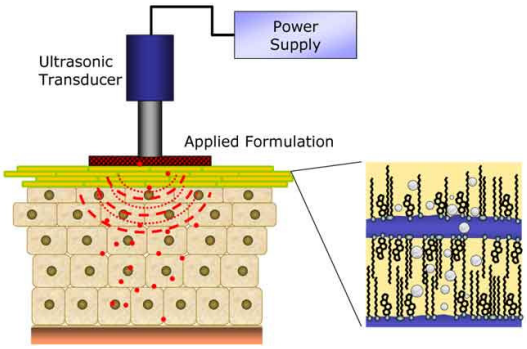


Fig:Schematic Expression of Drug Administration Facilitated By Ultra waves.

3. Photomechanical Waves

Photomechanical waves significantly led to the stratum cornea highly permeable to drug substance through a possible permeabilisation mechanism due to development of transient channels.

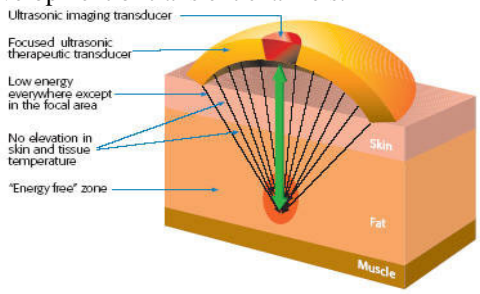


Fig:Schematic Expression of Drug Administration Facilitated By photochemical waves

4. Electroporation

It this method, short and high-voltage electrical pulses are applied to the skin thus the diffusion of drug is improved with the increasing permeability. The electrical pulses are considered to form small pores in the stratum cornea, through which transportation of drug occurs. For the safe and painless administration, the electrical pulses introduced by closely spaced electrodes to reserved the electric field within the stratum cornea.

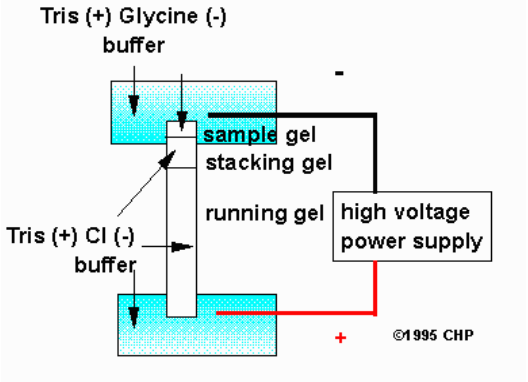


Fig: Schematic Expression of Drug Administration Facilitated By Electoporation

5. Electro-Osmosis

To the porous membrane which is having some charge, a voltage difference is applied to it, thus a bulk fluid or volume flow takes place with no concentration gradients. This process is known as electro-osmosis.

C) VELOCITY BASED ON ENHANCEMENT TECHNIQUES:

Needle-Free, InjectionsIntraject Implaject ,
Jet Syringe
Iject ,Mini-ject .

Powderject Device

The solid drug particles are propelled across the skin with the aid of high-speed gas flow. This consists of a gas canister that allows helium gas at high pressure to enter a chamber atthe end of which drug cassette containing powdered drug between two polycarbonate membranes. After release, the instantaneous rupturation of both membranes usually seen that results in the gas to expand quickly which forms a strong motion like a wave that travels down the nozzle. This takes place at the speed of 600-900 m/s.

D) OTHER ENHANCEMENT TECHNIQUES:

1. Transfersomes-

This device penetrates the skin barrier along the skin moisture gradient. Transfersome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug. Transfersomes contain a component that destabilizes the lipid bilayers and thus leading to the deformable vesicles.

2. Medicated Tattoos Med-Tats is a modification of temporary tattoo which contains an active drug substance for trandermal delivery. This technique is useful in the administration of drug in those hildren who are not able to take traditional dosage forms.

3. Skin Abrasion

This involves direct removal or disruption of the upper layers of the skin to provide better permeation of topically applied drug substance. In general, one approach is adopted to creates micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal ranules is generally known as Microscissuining.

4. Controlled Heat Aided Drug Delivery (CHADD)

System It facilitates the transfer of drug substance to the blood circulation by applying heat to the skin that increases the temperature and ultimately led to increase in microcirculation and permeability in blood vessel.CHADD system consists of small unit that is used for heating purpose, placed on top of a conventional patch device. An oxidation reaction occurs within the unit which tends to form heat of limited intensity and duration.

EVALUATION PARAMETERS OF NANOPARTICLE LOADED PATCH

1. Interaction studies:

Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug

2. Thickness of the patch:

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

3. Weight uniformity:

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

4.Folding endurance:

A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

5.Percentage Moisture content:

The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs.

After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

Percentage moisture = [Initial weight- Final weight/ Final weight] ×100 content

6.Percentage Moisture uptake:

The weighed films are to be kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.

Percentage moisture = [Final weight- Initial weight/ initial weight] ×100 uptake

7. Water vapour permeability (WVP) evaluation:

Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula

Where, WVP is expressed in gm/m2 per 24hrs,

W is the amount of vapour permeated through the patch expressed in gm/24hrs and A is the surface area of the exposure samples expressed in m2.

8. Drug content:

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

9.Uniformity of dosage unit test:

An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was alysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated.

10. Polariscope examination:

This test is to be performed to examine the drug crystals from patch by polariscope. A specific surface area of the piece is to be kept on the object slide and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch.

11. Shear Adhesion test:

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of crosslinking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength.

12-Peel adhesion test:

In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180º angle, and the force required for tape removed is measured.

13. Thumb tack test:
It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.

14. Flatness test:
Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

15. Percentage Elongation break test:
The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula.
Elongation percentage = L1-L2 ×100 L2
Where, L1is the final length of each strip and
L2 is the initial length of each strip.

16. Rolling ball tack test:
This test measures 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 down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

17. Quick Stick (peel-tack) test:
In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required to break the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

18. Probe Tack test:
In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.

19. *In vitro* drug release studies:
The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite 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 equilibrated to 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 withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

20. *In vitro* skin permeation studies:
An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor. compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or H LC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated mg cm2 vs. time.

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

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

CONCLUSION
Transdermal drug delivery system is useful for topical and local action of the drug. Due to large advantages of the transdermal drug delivery system and various permeation enhancers which would significantly increase the number of drugs suitable for transdermal drug delivery system, this system interests a lot of

researchers. Transdermal drug delivery system a realistic practical application as the next generation of drug delivery system.

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