



Review Article

TRANSDERMAL DRUG DELIVERY: AN OVERVIEW

Ashvini S. Kadam*, Mukesh P. Ratnaparkhi, Shilpa P. Chaudhary

Department of Pharmaceutics, Marathawada Mitra Mandal's College of Pharmacy, Thergaon, Pune.

*Corresponding Author: Email ashvinibpharm@gmail.com, mukeshparkhi@yahoo.com

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ABSTRACT

Much attention has been given in recent years with regard to the transdermal delivery devices. Broadly this system can be considered as single layer and multilayer. Fick's first law of diffusion is the principle of drug kinetics. As a substitute for the oral route Transdermal drug delivery enables the avoidance of gastrointestinal absorption, with its associated pitfalls of enzymatic and pH associated deactivation. Transdermal delivery has many advantages over conventional modes of drug administrations, it thus avoids hepatic first pass metabolism and improves patient compliance. Its main advantages include controlled drug release with minimum side effects, improved bioavailability, bypass first pass metabolism and many more. There are factors such as physicochemical as well as biological which affect the bioavailability of transdermal medicament. During the past decade, number of drugs formulated in the patches is hardly increased; there has been little change in the composition of the patch system. Modifications have been mostly limited to refinements of the materials used. The present review article explores the overall study on transdermal drug delivery system (TDDS) which leads to novel drug delivery system (NDDS).

Keywords: Transdermal, Drug kinetics, Drug delivery system.

INTRODUCTION

Oral route is the popular route of drug delivery. Although it has some disadvantages including first pass metabolism, drug degradation in gastrointestinal tract due to enzymes, pH etc. To cross these problems, a novel drug delivery system was developed (Chien, 1992; Banker, 1990; Guy, 1996). In this transdermal delivery system medicated adhesive patches are prepared which deliver therapeutically effective amount of drug across the skin when it is placed on skin. Medicated adhesive patches or transdermal patches are of different sizes, having more than one ingredient. Once they are applied on unbroken skin they deliver active ingredients into systemic circulation passing via skin barriers. A patch containing high dose of drug inside which is retained on the skin for prolonged period of time, which gets entered into blood flow via diffusion process. Drug can penetrate through skin via three pathways—through hair follicles, through

sebaceous glands, through sweat duct. Transdermal drug delivery systems are used in various skin disorders, also in the management of angina pectoris, pains, smoking cessation & neurological disorders such as Parkinson's disease.^(1,2)

Advantages of transdermal drug delivery system

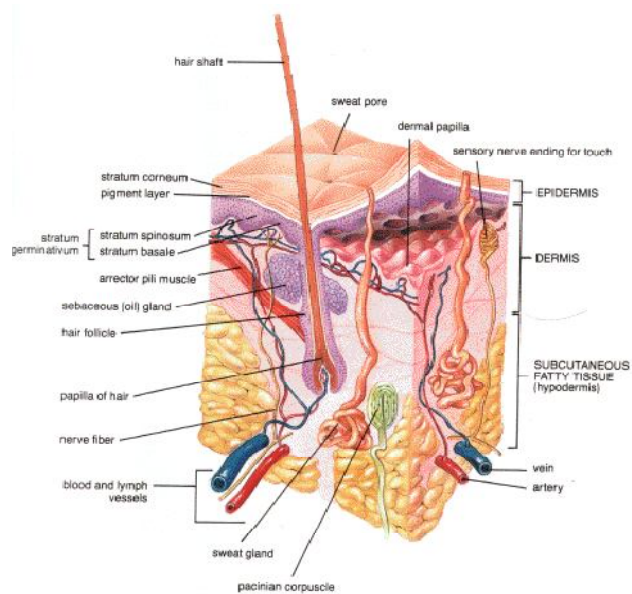
1. First pass metabolism of drug gets avoided.
2. Gastrointestinal incompatibilities get avoided.
3. Self medication is possible.
4. Duration of action gets extended & predictable.
5. Unwanted side effects get minimized.
6. Drug plasma concentration gets maintained.
7. Number of doses gets reduced which improves patient compliance.
8. Therapeutic value of many drugs gets increased by avoiding problems associated with drug like—lower absorption, GI irritation, decomposition due to hepatic first pass metabolism.^(3,4)

Disadvantages of Transdermal drug delivery System

1. Chances of allergic reactions at the site of application like-itching,rashes,local edema etc.
2. Larger molecular size of drug (above 1000)creates difficulty in absorption.
3. Barrier function of skin varies from site to site on the same or different person.
4. Drug with hydrophilic character is less suitable as compare to drug with lipophilic character because of their low permeability.(5)

ANATOMY & PHYSIOLOGY OF SKIN

The human skin is a multilayered organ composed of many histological layers. Skin is most accessible organ in body. Its major functions are; protection of major or vital internal organs from the external influences, temperature regulations, control of water output and sensation. The skin of an average adult body covers approximately surface area of two square meters and receives about one-third of the blood circulating through the body.



Human skin comprises of three distinct but mutually dependent tissues as given below

A) The stratified, vascular, cellular epidermis,

B) Underlying dermis of connective tissues

C) Hypodermis.

A) Epidermis- The epidermis is a stratified, squamous, keratinizing epithelium. The multilayered epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to

0.06 mm on the eyelids.90% epidermal cells are keatinocytes arranged in five layers & produce keratin protein.8% melanocytes are presents. They produce melanin-a yellow or brown black pigment that contributes to skin colour & absorbs damaging UV light. A Langerhans cell arises from red bone marrow & migrates to epidermis, where they constitute small fraction of epidermis cells. Markel cells are least numerous of epidermal cells. (6)

Five layers of epidermis-

- a) Stratum basale
- b) Spinosum
- c) Granulosum
- d) Lucidum
- e) Corneum

B) Dermis- It is 3 to 5mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerves. The dermis is the inner and larger (90%)skin layer, comprises primarily of connective tissue and provides supports to the epidermis layer of the skin. The boundary between dermis and epidermis layer is called Dermal- Epidermal junction which provides a physical barrier for the large molecules of drug and cells. The dermis incorporates blood and lymphatic vesicles and nerve endings. Dermis is divided into papillary & reticular region.(7)

1 Papillary region-It makes up one fifth of thickness of total layer, contain areolar connective tissue containing fine elastic fibers.

2 Reticular region-It is attached to subcutaneous layer; consist of dense irregular coactive tissue containing fibroblast, bundle of collagen & some coarce elastic fibers.

C) Hypodermis- The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanic al protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. The hypodermis layer is composed of loose connective tissues and its thickness varies according to the surface of body. (8)

FACTORS AFFECTING TRANSDERMAL DRUG DELIVERY

A) Physicochemical properties of permeate:

1. Partition coefficient

2. Molecular size
3. Solubility/melting point
4. Ionization

B) Physiological & pathological conditions of skin:

1. Reservoir effect of horny layer-
2. Lipid film
3. Skin hydration
4. Skin temperature
5. Regional variation
6. Pathological injuries to the skin
7. Cutaneous self-metabolism
8. Skin barrier properties in the neonate and young infant
9. Skin barrier properties in aged skin
10. Race
11. Body site
12. Penetration enhancers used(9)

A) Physicochemical properties of permeate-

1. Partition coefficient-

Water & lipid soluble drugs favorably absorbed through the skin. Intercellular route is applicable for drugs with intermediate partition coefficient ($\log K$ 1 to 3) & having high lipophilicity. The transcellular route probably predominates for more hydrophilic molecules ($\log K < 1$).

2. Molecular size-

There is an inverse relationship existed between transdermal flux and molecular weight of the molecule. The drug molecule selected as candidates for transdermal delivery tend to lie within narrow range of molecular weight (100-500 Dalton).

3. Solubility/melting point-

Lipophilicity is a desired property of transdermal candidates as lipophilic molecules tend to permeate through the skin faster than more hydrophilic molecules. Drugs with high melting points have relatively low aqueous solubility at normal temperature and pressure.

4. Ionization-

According to pH-partition hypothesis, only the unionized form of the drug can permeate through the lipid barrier in significant amounts.(10)

B) Physiological & pathological conditions of skin-

1. Reservoir effect of horny layer- The reservoir effect of horny layer which is deeper layer is due to irreversible binding of a part of the applied drug with the skin.

2. Lipid film-

The lipid film on the skin surface acts as a protective layer to prevent the removal of moisture from the skin and helps in maintaining the barrier function of stratum corneum.

3. Skin hydration-

Skin hydration can be achieved simply by covering or occluding the skin with plastic sheeting, leading to accumulation of sweat & enhance the penetration by opening the dense, closely packed cells of the skin and increase its porosity.

4. Skin temperature- Increase in skin temperature increases the rate of skin permeation this is due to availability of energy required for diffusivity.

5. Regional variation-

Differences in nature and thickness of the barrier of skin cause variation in permeability

6. Pathological injuries to the skin-

Injuries that disrupt the continuity of the stratum corneum, increases permeability due to increased vasodilatation caused by removal of the barrier layer

7. Cutaneous self-metabolism-

Catabolic enzymes present in the epidermis may render the drug inactive by metabolism and thus the topical bioavailability of the drug.

8. Skin barrier properties in the neonate and young infant-

The pH of skin surface of new borns is higher than those in adult skin. The skin surface of the newborn is slightly hydrophobic and relatively dry and rough when compared to that of older infants. Stratum corneum hydration stabilizes by the age of 3 months.

9. Skin barrier properties in aged skin-

There are changes in the physiology of aged skin (>65 years). The corneocytes are shown to increase in surface area which may have implications for stratum corneum function due to the resulting decreased volume of intercorneocyte space per unit volume of stratum corneum. The moisture content of human skin decreases with age

10. Race-

Racial differences between black and white skins have been shown in some anatomical and physiological functions of the skin although data is relatively sparse. In black skin,

increased intracellular cohesion, higher lipid content and higher electrical skin resistance levels compared to whites have been demonstrated.

11. Body site-

Skin structure varies at different sites of body. Genital tissue usually provides the most permeable site for transdermal drug delivery. The skin of the head and neck is also relatively permeable compared to other sites of the body such as the arms and legs. Intermediate permeability for most drugs is found on the trunk of the body.

12. Penetration enhancers used- Low permeability of drugs across the skin can be improved by the development of penetration enhancers. According to Chien et.al., penetration enhancers or promoters are agents that have no therapeutic properties of their own but can transport the sorption of drugs from drug delivery systems onto the skin and/or their subsequent transdermal permeation through skin.(11)

COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM

1. Polymer matrix/ Drug reservoir
2. Drug.
3. Permeation enhancers.
4. Pressure sensitive adhesive (PSA).

5. Backing laminate.
6. Release liner.
7. Other excipients like plasticizers and solvents(12)

1. Polymer matrix/ Drug reservoir-

Polymers are core part of TDDS.It is prepared by dispersing the drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers. Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status. Polymers used in TDDS are classified as-

- Natural polymers:
e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.
- Synthetic elastomers:
e.g. polybutadiene, hydrin rubber, silicon rubber, polyisobutylene, acrylonitrile, neoprene, butyl rubber etc.
- Synthetic polymers:
e.g. polyvinylalcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc.(13)

2. Drug-

Some of ideal properties of drug & some factors to be consider during preparation of TDDS are as follows-

Table: 1 Ideal properties of drug & some factors to be consider during preparation of TDDS

Parameters	Properties
Dose	Should be low (less than 20mg/day)
Half life	10/less(hrs)
Molecular weight	<400da
Skin permeability coefficient	>0.5*10 ⁻³ cm/h
Skin reaction	Non irritating non sensitizing
Oral bioavailability	Low

Table: 2 Factors to be considered for transdermal dose calculation-

Physicochemical	Pharmacokinetic	Biological
Solubility	Half life	Skin toxicity
Crystallinity	Volume of distribution	Site of application
Molecular weight	Total body clearance	Allergic reaction
Polarity	Therapeutic plasma concentration	Skin metabolosome
Meting point	Bioavailable factor	--

3. Permeation enhancers-

Chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate. They improve the permeability by interacting with structural components of stratum corneum.

Ideal properties of permeation enhancers-

1. They should be non-irritating, non toxic & non-allergic.
2. They should not bind to receptor site i.e. not showing any pharmacological activity.
3. They should be cosmetically acceptable with an appropriate skin feel.(14)

4. Pressure sensitive adhesive (PSA)-

Pressure sensitive adhesive helps to adhere transdermal patch to the skin surface. It can easily remove from the smooth surface without leaving a residue on it.

Ex-Polyacrylates, polyisobutylene and silicon based adhesives are widely used in TDDS.

5. Backing laminate-

Backing laminates are supportive material which is impermeable to drugs and also to permeation enhancers. They should be chemically compatible with the drug, enhancer, adhesive and other excipients.

Ex-vinyl, polyethylene and polyester films (15)

6. Release liner-

Release liner is the primary packaging material that can protect the patch which will remove during application of patch to the skin. Release liner is made up of base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or Teflon. Release liner should be chemically inert & it should be permeable to drug, penetration enhancers & water.

7. Other excipients like plasticizers and solvents-

Solvents used are chloroform, methanol, acetone, isopropanol and dichloromethane. Plasticizers used dibutylphthalate, triethylcitrate, polyethylene glycol and propylene glycol.(16)

TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM

A. Reservoir System-

In drug this System the drug reservoir is kept in between backing layer and a rate controlling membrane. Drug releases through microporous rate controlled membrane. Drug can be in the form of a solution, suspension, or gel or

dispersed in a solid polymer matrix in the reservoir compartment.

B. Matrix System-

1. Drug-in-adhesive system- For the formation of drug reservoir drug dispersed in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in the case of hot-melt adhesives) onto an impervious backing layer.

2. Matrix-dispersion system-

In matrix-dispersion system the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. Then this containing polymer along with drug is fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing layer. Adhesive is spread along the circumference instead of applying on the face of drug reservoir to form a strip of adhesive rim.(17)

C. Micro-Reservoir System -

This system a combination of reservoir and matrix-dispersion systems. Here drug is suspended in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unleachable, microscopic spheres of drug reservoirs.(18)

METHODS OF PREPARATION OF TDDS

1. Asymmetric TPX membrane method
2. Circular Teflon mould method
3. Mercury substrate method
4. By using "IPM membranes" method
5. By using "EVAC membranes" method
6. Preparation of TDDS by using Proliposomes
7. By using free film method

1. Asymmetric TPX membrane method- (Berner and John 1994)

By this method prototype patch can be prepared by using heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter as the backing membrane. Drug dispersed on concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive.

Asymmetric TPX membrane preparation:

These are prepared by using the dry/wet inversion process. Here TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°C to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a

glass plate. Then casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs].

2. Circular Teflon mould method-(Baker and Heller 1989)

Polymeric solution in various ratios is used as an organic solvent. Then that solution is divided in two halves. In one half calculated amount of drug is dissolved & in another half enhancers in different concentration are dissolved, and then two halves mixed together. Plasticizer (e.g., Di-N-butylphthalate) is added into the drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular Teflon mould. The moulds are to be placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 h. The dried films are to be stored for another 24 h at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects.

3. Mercury substrate method-

In the polymeric solution drug & plasticizer get dissolved. It is kept for 10-15min stirring to produce homogenous dispersion then it is poured into leveled mercury surface, covered with inverted funnel to control solvent evaporation.

4. By using "IPM membranes" method-

In the mixture of water & polymer (propylene glycol containing Carbomer 940 polymer) drug get dispersed and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. If the drug solubility in aqueous solution is very poor then solution gel is obtained by using Buffer pH 7.4. The formed gel will be incorporated in the IPM membrane.

5. By using "EVAC membranes" method-

For the preparation of target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is insoluble in water then use propylene glycol for gel preparation. Drug is dissolved in propylene glycol, carbopol resin will be added to the above solution and neutralized by using 5% w/w

sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

6. Preparation of TDDS by using Proliposomes-

By carrier method using film deposition technique proliposomes are prepared. Drug and lecithin ratio should be 0.1:2.0 taken as an optimized one from previous references. For the preparation of proliposome in 100ml round bottom flask take 5mg of mannitol powder, then it is kept at 60-70°C temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are placed in a desiccator over night and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.

7. By using free film method-

Cellulose acetate free film can be prepared by casting on mercury surface. 2% w/w polymer solution is prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution. (19,20)

EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM-

1. Interaction Studies

2. Thickness of the patch
3. Weight of uniformity
4. Folding endurance
5. Percentage moisture content
6. Percentage moisture uptake
7. Watervapour permeability (WVP)evaluation
8. Drug content
9. Uniformity of dosage unit test
10. Polaroscope evaluation
11. Shear adhesion test
12. Peel adhesion test
13. Thumb tack test
14. Flatness test
15. Percentage elongation break test
16. Rolling ball tack test
17. Quick stick (peel tack) test
18. Probe tack test
19. In vitro drug release studies
20. In vitro skin permeation studies
21. Skin irritation test
22. Stability studies-

1. Interaction Studies-

To produce stable product the drug & excipient must be compatible with each other. Drug-excipient interaction will affect the stability & bioavailability of the final formulation. When excipients are new, firstly used with the active substance in the formulation in that condition compatibility or interaction study is very much important. Interaction studies are carried out by Thermal analysis, Fourier transform infrared spectroscopy (FTIR), ultra violet (UV) and chromatographic techniques by comparing their physicochemical properties like assay, melting point, wave numbers, and absorption maxima

2. Thickness of the patch-

At different points the thickness of the patch is measured by using digital micrometer & determine average thickness & standard deviation of the same.

3. Weight of uniformity-

Before testing the patch is dried at 60 °C for 4 hrs. Cut that patch in different parts & weighed in digital balance. Take average weight & calculate standard deviation from individual weight.

4. Folding endurance-

A strip is cut with specific area. Fold that strip repeatedly at specific point till it get break. The number of times strip film get break gives the value of folding endurance.

5. Percentage moisture content-

Patch or film is weighed first then it is kept in desiccator containing calcium chloride at room temperature. Taken it out after 24hrs again reweighed & percentage moisture content is calculated by following formula-

Percentage moisture content (%) = $\frac{[\text{Initial weight} - \text{Final weight}]}{\text{Final weight}} \times 100$

6. Percentage moisture uptake-

Patch is weighed individually then it is kept in desiccator containing saturated solution of potassium chloride in order to maintain 84% Rhesus factor (RF) then film is reweighed & percentage moisture uptake is calculated by using following formula-

Percentage moisture uptake (%) = $\frac{(\text{Final weight} - \text{Initial weight})}{\text{Initial weight}} \times 100$

7. Water vapour permeability (WVP) evaluation-

The WVP can be determined by the following formula

$$\text{WVP} = \frac{W}{A}$$

Where, WVP is expressed in g/m² per 24 h, W is the amount of vapour permeated through the patch expressed in g/24 h, A is the surface area of the exposure samples expressed in m².

8. Drug content-

Take the patch with specific area dissolve it in specific volume of solvent. Solution is then filtered and the drug content analyzed with the suitable method (UV or HPLC technique). Then take the average of three different samples.

9. Uniformity of dosage unit test-

Take ten patches and content determined for individual patches. If 9 out of 10 patches have content between 85 to 115% of the specified value and one has content not less than 75 to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75 to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85 to 115%, then the transdermal patches pass the test.

10. Polaroscope evaluation-

This examination determines whether drug is present as amorphous or crystalline form in the final formulation by using polaroscope. Patch with specific surface area is kept on the object slide & observed for drug crystals.

11. Shear adhesion test- This test determines cohesive strength of adhesive polymer. Factors affecting are type & composition of polymers, its molecular weight, the degree of crosslinking & 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 its pulling in direction parallel to the plate. Shear adhesion test is determined by measuring the time it takes to pull the tape off the plate. The longer the time takes for removal, greater is the shear strength.

12. Peel adhesion test-

Here peel adhesion is the force required to remove an adhesive coating from a substrate. A single tape is applied to a stainless steel plate then tape is pulled from the substrate at a 180° angle, and the force required to pull the tape is measured.

13. Thumb tack test-

This test determines the tack property of adhesive. Thumb is pressed on adhesive & tack property is determined.

14. Flatness test-

Three longitudinal strips are cut from different portions of the films. The length of each strip is measured and the variation in length because of non-uniformity in flatness is measured by determining percentage constriction, with 0% constriction equivalent to 100% flatness

15. Percentage elongation break test-

Percentage elongation can be determined by using following formula-

$$\text{Elongation percentage} = \frac{L1 - L2}{L2} \times 100$$

Where L1 is the final length of each strip & L2 is the initial length of each strip.

16. Rolling ball tack test-

This test determines the softness of the polymer that relates to the tack. Here the stainless steel ball of size 7/16 inches in diameter is released on an inclined track so that it rolls down & comes in contact with horizontal, upward facing adhesive. Distance travelled by ball along adhesive track gives the measurement of tack expressed in inch.

17. Quick stick (peel tack) test-

Here the tape is pulled away from the substrate at 90°C 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 gms per inch width.

18. Probe tack test-

Here the probe with specific surface is kept in contact with adhesive so as to form bond between them. Then probe is removed so that it mechanically breaks it. The force required to pull the probe is the tack measured in terms of grams.

19. In vitro drug release studies

For the assessment of the release of the drug from the patches the paddle over disc method (USP apparatus V) can be used. Here the film with defined thickness, shape taken, weighed, fixed over glass plate attached with adhesive. It is kept in 500ml phosphate buffer (pH 7.4) as dissolution media & set the apparatus at 32±0.5°C. Keep the paddle at a distance 2.5cm from the glass plate & operated at a speed of 50rpm. 5ml of sample can be withdrawn at specific time interval for 24hrs & analysed by UV or HPLC. Perform the experiment in triplicate.

20. In vitro skin permeation studies-

By using diffusion cell in vitro skin permeation study is carried out. Here use of male wistar rat weighing 200-250gm. Take the abdominal skin of rat by removing the hairs from abdominal region by using electric clipper. Then dermal side of the skin is washed with distilled water to remove adhesive tissues then it is kept in dissolution media or phosphate buffer pH 7.4 for 1hr. before starting the experiment & was placed on magnetic stirrer with small magnetic needle for uniform distribution of diffusant. The temperature of cell was maintained at 32±0.5°C using thermostatically controlled heater. Rat skin is placed between the compartment of diffusion cell with epidermis facing in upward into donor compartment. Specific amount of volume is withdrawn from receptor compartment at specific time interval & equal volume of fresh sample is added. Withdrawn sample is filtered & analysed by UV or by using HPLC. Flux can be determined by plotting the slope between steady state values of the amount of drug permeated mg cm² vs. time in hours & permeability coefficient were deduced by dividing the flux by initial drug load mg cm².

21. Skin irritation test-

This study is performed on healthy rabbits (average weight 1.2-1.5kg). Remove the dorsal surface of rabbit by shaving & clean by using spirit. Formulation applied on skin surface & remove after 24hrs & skin is to be observed & classified in to 5 grades on the basis of severity of skin injury.

22. Stability studies-

Stability studies were done as per ICH guidelines where TDS samples are stored at $40 \pm 0.5^\circ\text{C}$ and $75 \pm 5\%$ RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyzed suitably for the drug content (Singh et al., 1993). (1,21,22)

RECENT TECHNIQUES FOR ENHANCING TDDS

A) Structure-Based Enhancement techniques

1. Transdermal Patches
2. Micro fabricated Micro needles
3. Macro flux
4. Metered-Dose Transdermal Spray (Mdts)

B) Electrically-Based Enhancement Techniques

1. Iontophoresis
2. Ultrasound
3. Photomechanical Waves
4. Electroporation
5. Electro-Osmosis

C) Velocity Based Enhancement techniques

1. Needle-Free Injections
2. Powderject Device

D) Other Enhancement Techniques

1. Transfersomes-
2. Medicated Tattoos-
3. Skin Abrasion-
4. Controlled Heat Aided Drug Delivery (CHADD)

System-

5. Laser Radiation-
6. Magnetophoresis-

A) Structure-Based Enhancement Techniques-

1. Transdermal Patches-

These are the medicated adhesive patch which delivers a specific dose of medication through the skin and into the bloodstream when placed on skin.

Components of TDDS-

1. Liner –

It protects the patch during storage & it can remove before use.

2. Drug –

Drug solution is in direct contact with release liner

3. Adhesive – It adhere the components of the patch together along with adhering the patch to the skin. E.g.- Acrylic, polyisobutylene (PIB), and silicone

4. Membrane –

Release of the drug from the reservoir and multi-layer patches is controlled by membrane.

5. Backing –

Protects the patch from the outer environment

Types of Transdermal patches

- a. Single layer Drug-in-adhesive-

Here the adhesive layer containing the drug is not only serves to adhere the various layers together but with the entire system to the skin. It is responsible for the releasing of the drug.

- b. Multi-layer Drug-in-Adhesive-

Here both adhesive layers are also responsible for the releasing of the drug. The multilayer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane

- c. Reservoir System-

Here drug reservoir is embedded between an impervious backing layer and a rate controlling membrane which is microporous or nonporous & release the drug. Drug is in the form of solution, suspension, gel or dispersed in a solid polymer matrix in drug reservoir compartment. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with the drug.

- Micro reservoir system-

This system is combination of reservoir and matrix system. The drug reservoir is formed by suspending the drug in an aqueous solution of water soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs.

- d. Vapour Patch-

In this the adhesive layer serves to adhere the various layers together but also to release vapour.

These patches release essential oils for up to 6 h which are responsible mainly used only in cases of decongestion mainly.

e. Matrix system

• Drug in adhesive system-

Here drug is dispersed in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting (in the case of hot melt adhesive) on an impervious backing layer. Unmediated adhesive polymer layers applied on the top of reservoir for protection purpose.

• Matrix dispersion system-

In this type the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

2. Microfabricated Microneedles

These devices having the combination features of hypodermic needle and transdermal patch that can deliver the drug that transports the drug effectively across the membrane. The systems consist of a drug reservoir and some projections (microneedles) extending from the reservoir, these help in penetrating the stratum corneum and epidermis to deliver the drug.

Different microneedles TDDS. These include –

• Poke with patch approach-

Involves piercing into the skin followed by application of the drug patch at the site of treatment.

• 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.

• Hollow microneedles-

Involves injecting the drug through the needle with a hollow bore.

3. Macroflux

Area of macroflux is around 8cm² as well as 300 micro projections per cm² with the length of individual micro projection less than 200µm.

Types of Macroflux –

a. Dry-Coated Macroflux system-

It consists of microprojection array coated with medicament that adhered to an elastic polymer adhesive backing & used for short period.

b. D-TRANS Macroflux system-

It consists of a microprojection array combined with reservoir of drug & also used for short period of time.

c. E-TRANS Macroflux system-

This is for on demand delivery that involves a microprojection array combined with an electrotransport system.

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 .

Advantages of MDTS-

Easy manufacturing

Dose flexibility

It improves delivery potential without skin irritation due to its non-occlusive nature.

• Increased acceptability.(23)

B) Electrically-Based Enhancement Techniques

1. Iontophoresis

Electrodes are kept in contact with formulations that have to be administered, passing the current through the skin. Ex- Pilocarpine delivery.

2. Ultrasound – (Sonophoresis and phonophoresis)

Here ultrasonic energy enhances the transdermal delivery of solutes either simultaneously or via pre-treatment and is frequently referred to as sonophoresis or phonophoresis. Drug mix with coupling agent (usually with gel, cream or ointment) that causes ultrasonic energy transfer from the system to the skin. Lipid present in stratum corneum get ruptured which allows the medicament to permeate via biological barrier.

3. Photomechanical Waves-

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

4. Electroporation-

Diffusion of drug is improved with the increasing permeability by applying the short and high-voltage

electrical pulses are applied to the skin. That impulse creates small pores in the stratum corneum, through which transportation of drug occurs.

5. Electro-Osmosis

In this method voltage difference is applied to porous membrane containing some charge. Volume flow takes place with no concentration gradients.^(24,25)

C) Velocity Based Enhancement Techniques

1. Needle-Free Injections-

- Intraject
- Implaject
- Jet Syringe
- Iject
- Mini-ject

2. Powderject Device-

In this device the high-speed gas flow propelled solid drug particles across the skin. This device consists of two parts: drug cassettes and gas canister. Drug cassettes contain powdered drug between two polycarbonate membranes and gas canister attached to drug cassettes which contain helium gas under pressure. After release, both membranes get ruptured and gas expands 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.^(26,27)

D) Other Enhancement Techniques

1. Transfersomes-

A novel vesicular drug carrier system called transfersomes, which contain phospholipids, surfactant, and water for enhanced transdermal delivery. Transfersome penetrates the skin barrier along the skin moisture gradient and creates a drug depot in the systemic circulation that is having a high concentration of drug.

2. Medicated Tattoos-

These tattoos contain an active drug substance for transdermal delivery. It is useful in the administration of drug in those children who are not able to take traditional dosage forms.

3. Skin Abrasion-

For providing better permeation of topically applied drug substance the upper layer of skin gets ruptured. In skin abrasion microcirculation where microchannels are created in the skin by eroding the impermeable outer layers with sharp microscopic metal granules.

4. Controlled Heat Aided Drug Delivery (CHADD) System-

In this system heat is applied to the skin which facilitates the transfer of drug substance to the blood circulation. Temperature of skin gets increased and ultimately it led to increase in microcirculation and permeability in blood vessel.

5. Laser Radiation-

In this technique ablation of the stratum corneum without damaging the epidermis which remains in contact with it by exposure of laser radiation to the skin. Removal of the stratum corneum by this technique is considered to improve the delivery of lipophilic and hydrophilic drugs.

6. Magnetophoresis-

Magnetic field is applied on diffusion flux of drug substance was found to be enhanced with increasing applied strength.^(28,29)

CONCLUSION

Transdermal drug delivery system is a novel drug delivery system which gives an assurance that the pharmacologically active substance gives desired effect at target site with minimum side effects. Transdermal drug delivery system also overcomes the problems associated with current drug delivery system, thus it has a promising future.

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