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An Overview on Transdermal Drug Delivery System

Vijay Bahadur Maurya, Vinay Kumar, Rajeev Kumar

1- Dept. of Pharmacy, V. B.S. Purvanchal University, Jaunpur, U.P.

2- Dept. of Pharmacy, V. B.S. Purvanchal University, Jaunpur, U.P.

3- Dept. of Pharmacy, V. B.S. Purvanchal University, Jaunpur, U.P.

ABSTRACT

Transdermal drug delivery is involved in the transportation of drug through the skin for systemic circulation. Now a day's more than 74% of drugs are administered drug in the form of tablet, capsule, which are taken orally but sometimes those are not effective as desired due to physiological activities of body. The major obstruction caused by stratum corneum to penetrate the drug. So there is need to facilitate the stratum corneum to increase the flux, a number of approaches are used to enhance the penetration of drug. Transdermal drug delivery system (TDDS) are very effectively overcome the hepatic first pass metabolism and improve the steady plasma drug concentration. The present review article provides an overview of various types of transedrmal patches, method of preparation and their evaluation.

Keywords- Transdermal drug delivery system, First pass metabolism, TDDS

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***Address for Correspondence:**

Vijay Bahadur Maurya, Department of Pharmacy, V. B. S. Purvanchal University, Jaunpur, U.P.

Introduction-

Transdermal drug delivery is one of the most approachable controlled drug delivery system by which we can topically administered medicament in the form of patches by which drugs are delivered for systemic circulation with a controlled rate. The TDDS offers many advantages upon conventional dosage form including more patient compliance, elimination of hepatic first pass metabolism, more uniform plasma level, prolong action to reduce the dosing frequency.

Advantages of transdermal drug delivery system[1,2]:

1- Ease of handling, self-administration is possible.

2- Avoid the first pass metabolism of drug.

3- In case of any adverse action, it can be easily discontinued by simply detaching the patches.

4- Avoid the interaction of drug with gastro-intestinal fluid and other medication, thus improve the bio-availability.

5- A predetermined and stable drug plasma concentration of drug can be achieved.

6- It is easy to applicable in nauseated or unconscious patient.

7- The patches can be designed for prolong action. It may ranges from few hours to weeks.

Disadvantages of transdermal drug delivery system[3]:

1- Sometime drug or excipient may cause the skin irritation.

2- Drugs with hydrophilic characteristic are slowly permeate through stratum corneum.

3- Due to variable thickness of skin from one place to another or with age, the permeability of drug is affected.

4- It is costlier than conventional dosage form.

5- Higher molecular weight of drug (>500Da) is usually difficult to cross the stratum corneum.

Component of transdermal drug delivery system:

(1) Polymer Matrix[4,5,6,7]:- Polymers are the base of TDDS that manage the release of drug from the devices. The drug and other excipient are embedded in Polymer matrices and that can be prepared by dispersion. Hence

the polymer should be stable, nontoxic, inexpensive, compatible with wide variety of drug molecule and excipients, that are easily facilitate the diffusion of drug from the matrices with desired rate and also capable of consist large amount of drug material.

Types of polymer-:

Natural polymer:- Zein, shellac, gelatin, cellulose derivatives, chitosan, gum, natural rubber etc.

Synthetic elastomer:- Poly-butadiene, nitrile, acrylonitrile, silicon rubber, neoprene, butyl rubber, etc.

Synthetic polymer:- Hodroxy propyl methyl cellulose, polyvinyl pyrrolidine, polyvinyl chloride, polyvinyl acetate, polyacrylate, poly propylene, poly urea, poly methyl metha acrylate, ethyl cellulose, eudragit etc.

(2) Drug[8,9]:- The suitable choice of drug is based on the phisico- chemical and pharmaco-kinetic properties. Which are basically daily dose of drug should be less than 5 mg/day, molecular weight should be less than 500 dalton, log P value varying from 1-3, drug should have short biological half lives, extensive first pass metabolism..

(3) Permeation enhancer[10,11]:- Permeation enhancer promotes the transportation of the drug from the patch to the skin. Permeation enhancers are act by altering the barrier properties of skin by improved fluidity of membrane structure or by facilitation of drug solubility within the skin. These permeation enhancer are characterized as chemical and physical method of enhancement.

(a)- Chemical enhancer:- Sulfoxide like DMSO, alcohols, polyols like propylene glycol, fatty acid like oleic acid, esters like ethyl acetate, amines like urea, terpenes both mono and di sesquiterpenes and surface active agents – both anionic like SLS and cationic like pluronic F 127.

(b- Physical Enhancer[12]:-Physical enhancement is based on electrical techniques like electroporation, phonophoresis, iontophoresis etc. and velocity based devices like liquid jet injection.

(4) Other Excipients[13,14]:-

(a): Adhesive:- The pressure sensitive adhesive helps in fastening of the device to the skin which is positioned on the face or back of the device. It should possess the following characteristics-

- It should aggressively stick to the skin surface.
- It should easily peel off and dosen·t leave any leftover on the skin.
- It should be physically and chemically compatible with drug and excipients.
- It should not cause sensitization to the skin.
- In case of face adhesive system the drug permeation should not affected.

(b): Backing Laminate[15,16]: The backing laminate protect the patch from outer environment. It should have the low water transmission rate to facilitate the hydration of skin by which increase the solubility and permeation of medication. Backing laminate also should be compatible with drug and other excepients and having a great rigidity. For example poly vinyl acetate, poly propylene, cellulose derivatives etc.

(c): Release liner[17]: release liners are responsible to protect the patch during storage. It should be removed before the application of patch. Because of the liner is in contact to the patch it should comply the chemical inertness.

Types of formulation of TDDS:

(A): **Adhesive dispersion type system[18]:** Such a system polymer reservoir is fabricated by dispersing drug in adhesive polymer, which is then pour on flat sheet of drug impermeable metallic plastic backing membrane through solvent casting or hot melting to obtain drug reservoir. The drug reservoir layer is then covered by a non-medicated rate controlling adhesive polymer membrane to produce an adhesive diffusion controlled drug delivery system.

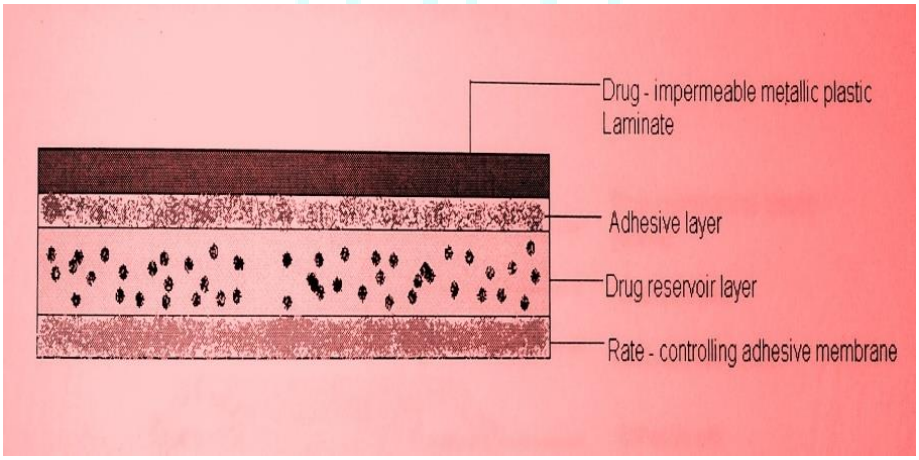

Fig-1. Adhesive diffusion controlled transdermal drug delivery system

(B): **Membrane permeation controlled system[18,19,20]:** In this the drug is homogeneously dispersed in solid polymer matrix to fabricate the reservoir, it is the either dissolved in a releasable solvent to form a gel like or suspended in a unleachable viscous liquid medium to form a gel like suspension and then completely enclosed in a compartment molded between a drug impermeable metallic plastic backing laminate and a rate controlling polymeric membrane.

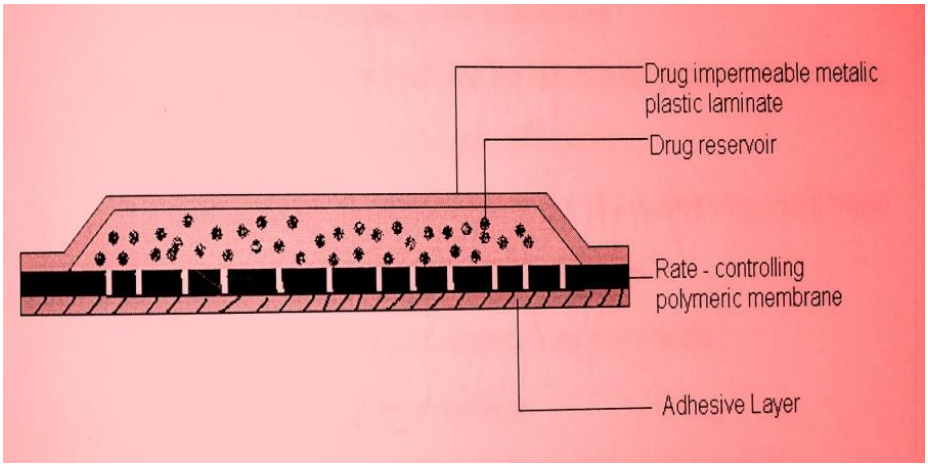

Fig-2. Membrane moderated transderml drug delivery system

(C): **Matrix diffusion controlled system[8,14]:** The drug is diffused homogeneously in a hydrophilic polymer matrix. This drug embedded polymer matrix is then fixed on an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing laminate. The adhesive is spread along the circumference of drug reservoir to form a adhesive rim.

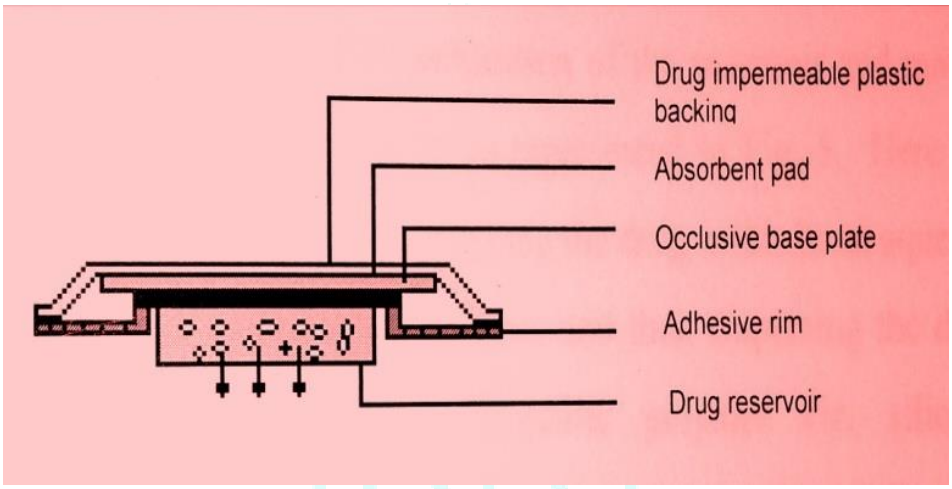

Fig-3. Matrix diffusion controlled transdermal drug delivery system

(D): **Microreservoir type controlled system[4,18,21,22]:** This kind of TDDS is a combination of reservoir and matrix dispersion system. The drug reservoir is prepared by first suspending the drug in solution of water soluble polymer and then dispersing the formed drug suspension in a hydrophobic polymer homogeneously to form thousands of unleachable microscopic spheres of drug reservoir.These formulated dispersion are thermodynamically unstable and stabilized by crosslinking of polymer.

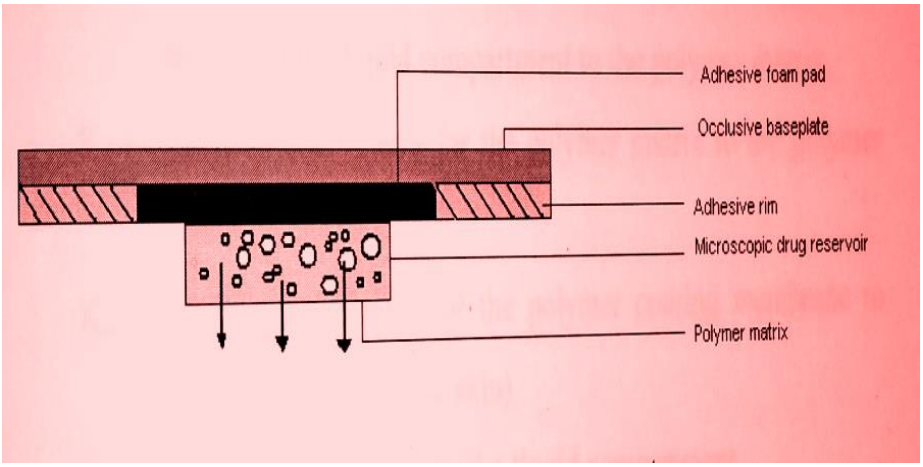

Fig- 4. Microreservoir controlled Transdermal drug delivery system

Various methods of preparation of TDDS-

(A): Circular Teflon mould method[19,22,23,24,25]- In this method blend of polymers in various ratio are used in organic solvent. This polymer solution is divided in two equal halves, in one half of polymer solution the calculated amount of drug is dissolved and enhancer is added in another half of polymer solution. Now these two halves are mixed in one another and plasticizers is added to this and stir for 12 hours and then poured in to a circular Teflon moulds. These moulds are placed on a horizontal plane surface and covered with inverted funnel to limit the evaporation of solvent in a laminar flow hood for 24 hours with an air speed 0.5 m/s. The dried films are to be stored in a desiccators containing silica gel for another 24 hours at 25 ±0.5^{0}C.

(B): Mercury substrate method[19,22,26]**:** In this method took the drug along with plasticizer and dissolved in polymer solution. The solution is to be stirred for 10 - 15 minutes to produce a homogeneous dispersion and discharged in to a horizontal plane mercury surface and covered with an inverted funnel to limit the solvent evaporation.

(C): By using EVAC membrane method[27,28]**:** In order to prepare the target transdermal therapeutic system, 1% carbopol is used to form the reservoir gel and polyethylene, ethylene vinyl acetate copolymer membrane can be used as rate controlling membrane. Propylene glycol may be used for insoluble drug to prepare the gel. Drug is dissolved in propylene glycol, carbonyl resin is added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The medicated gel is poured on a sheet of backing layer occupying the specified area. The rate controlling membrane is placed on medicated gel and the edges will be sealed to prevent escaping of the gel by heat to obtain a leak proof device.

(D): By using IPM membrane method[29,30]**:** In this method a mixture of water and propylene glycol containing carbomer 940 polymer is prepared and the drug is dispersed in it and stirred for 12 hours on magnetic stirrer. The dispersion is neutralized and made viscous by addition of triethanolamine. The formed gel will be incorporated in the IPM (isopropyl myrstitate membrane).

(E): Aluminium backed adhesive film method[28,31]**:** When the loading dose of drug is more than 10mg the transdermal drug delivery system may produce unstable matrices, then drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custammade aluminium film former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

(F): Prepartion of TDDS by using proliposomes[28,32,33]: Proliposomes are prepared by adding 5 mg mannitol in 100ml round bottom flask which is kept at 60-70^{0}c temp and flask is rotated at 80-90 rpm and dried in vaccum for 30 minutes. After drying the temp of water bath is adjust to 20-30^{0}C. Drug and lecithin in ratio of (0.1:2.0) dissolved in suitable organic solvent. A 0.5ml aliquot of organic solution is added to rbf at 37^{0}C and second aliquot (0.5 ml) of organic solution is added after complete drying. After the last loading, the flask connected to the lyophilizer. The prepared proliposomes placed in dessicator for overnight and passed through 100 mesh sieve and stored in glass bottle at freeze temperature.

Evaluation of transdermal patch:

(1) **Thickness of patch**[23,34,35,36]**:** The thickness of patch is measured at different places with the help of digital micrometer or screwgauze and determine the average thickness of the film.

(2) **Weight uniformity test**[34,35,36]**:** For the weight variation patches are selected randomly and dried at 60^{0}C for 4 hours. Each patches are weighed individually and calculate the average weight. The individual weight should not deviate from average weight.

(3) **Moisture content test**[35,36,37,38]**:** The prepared patches are weighed individually and place in a desiccators containing calcium chloride at room temperature for 24 hours or activated silica for 12 hours. The patches are weighed again after a specified period of time till the patches does not show a constant weight. It is measured by the formula:

$$\% \text{ moisture content} = \frac{(\text{Initial weight} - \text{Final weight})}{(\text{Final weight})} \text{x}100$$

(4) **Folding endurance** [34,35,36,39]**:** The prepared patch is folded at a place repeatedly till it has broken. The numbers of times folded at the same place without breaking gives the value of folding endurance.

(5) **Drug Content Uniformity** [28,40]**:** The specified area of patch is dissolved in suitable solvent and shaken continuously for 24 hours. Then the solution is filtered through filter media and after making a suitable dilution the solution is estimated spectrophotometrically.

(6) **Water absorption test**[35,36,40]**:** Weighed films were kept in a desiccators at room temperature for 24 hours. These were then exposed to saturated solution of Potassium chloride in order to maintain 84% relative humidity until a constant weight is attained. The percentage moisture uptake is calculated by formula:

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

(7) **Shear adhesion test**[22,34,36]**:** The shear strength of an adhesive polymer is depend on cohesive property of polymer, Which can be influenced by molecular weight, composition of polymer, degree of cross linking and the type of amount of tackifier added. In this an adhesive coated tape is applied on to stainless steel plate, a specified weighed is hung from the plate. Shear adhesion strength is determined by measuring the time it takes to pull off the tape from the plate. More the time taken, greater the shear strength.

(8) **Peel adhesion test**[22,34,36]**:** Force required to detach an adhesive coating from a test substrate is called peel adhesion. The force required can be influenced by molecular weight, type and amount of adhesive added. In this test force require for removal of tape is measured by applying a single tape to stainless steel and then the tape is pulled from the substrate at 180^{0}angle.

(9) **Water vapour transmission rate**[35,36,39]**:** water vapour transmission rate is determined by placing saturated solution of potassium chloride in a desiccators and the whole assembly is kept for three days to achieve the humid condition above 80% RH. Glass vials of equal diameter taken and to this filled one gram of fused calcium chloride. Then patches are fixed over the brim of vials with the help of adhesive like silicon adhesive grease and the vials accurately weighed. These vials are then placed in the desiccators maintained at 80% RH. Weight gained due to water vapour transmission through the film obtained by

weighing these vials every 24 hours for seven days. The transmission rate is calculated by using formula-

$$\text{Transmission rate} = \frac{(W \times L)}{(S)}$$

W= water transmitted in gram

L= Thickness of film

S= Exposed surface area

(10) **In Vitro Drug release[36,39,41]:** The paddle over disc apparatus (USP apparatus V) can be employed for assessment of release of drug from the prepared patch. The patches of definite weight are fixed over a glass plate with an adhesive. The glass plate is placed in dissolution medium and apparatus is equilibrated at 32±5^{0}C. The paddle is set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. The sample is withdrawn at appropriate interval and after suitable dilution the absorbance is determine spectrophotometrically.

(11) **In- vitro skin permeation studies[27,39,41]:** in vitro permeation studies can be performed by using diffusion cell like franz diffusion cell or keshary- chien diffusion cell. The receptor compartment is filled with dissolution medium phosphate buffer saline pH 7.4 and is placed on magnetic stirrer with magnetic needle for uniform distribution of medium. The temperature is maintained at 32±0.5^{0}C by using thermostat. The isolated rat skin is sandwiched between donor and receiver compartment of diffusion cell with the stratum corneum facing towards donor compartment side. A sample of definite volume is withdrawn at regular interval from the receiver compartment and equal volume of phosphate buffer saline is replaced. Sample are to be filtered through filtering media and analyzed spectrophotometrically or HPLC.

Conclusion:

TDDS provide a technology by which drug can be placed at the site of action without rupturing the skin By using polymer and penetration enhancer the system is able to transport the sufficient amount of drug to elicit the pharmacological response. This drug delivery overcomes the challenges associated with current drug delivery and it shows a promising future.

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