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Transdermal Patch of Anti-Diabetic Drug

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In the present work, monolithic matrix transdermal systems containing Drug x were prepared using various ratios of the polymer blends of hydroxy propyl methyl cellulose (HPMC) and Eudragit S 100 (ES) with triethyl citrate as a plasticizer. A 32 full factorial design was employed. The concentration of HPMC and ES were used as independent variables, while percentage drug release was selected as dependent variable. Physical evaluation was performed such as moisture content, moisture uptake, tensile strength, flatness and folding endurance. *In-vitro* diffusion studies were performed using cellulose acetate membrane (pore size 0.45 μ) in a Franz's diffusion cell. The concentration of diffused drug was measured using UV-visible spectrophotometer (Jasco V-530) at λ max 269 nm. The experimental results shows that the transdermal drug delivery system (TDDS) containing ES in higher proportion gives sustained the release of drug.

Keyword: HPMC, Eudragit S 100, Drug x, Transdermal Delivery.

1. Introduction

1.1 Introduction to Transdermal Drug Delivery System

1.1.1 Controlled drug delivery system[1,2]

Treatment of chronic and acute disease has been accomplished by delivery of drug to patient using various pharmaceutical dosage forms. These dosage forms are known to provide a prompt release of drug. But recently several technical advancements has been done and resulted in new techniques for drug delivery. These techniques are capable of controlling the rate of drug release. The term-controlled release has a meaning that goes beyond scope of sustained release. The release of drug ingredients from a controlled release drug delivery advances at a rate profile that is not only predictable kinetically, but also reproducible from one unit to another. The difference between sustained release and controlled release is shown in **Fig. 1**.

The classification of controlled drug delivery can be given as follows:

1. Rate-preprogrammed drug delivery systems
2. Activation-modulated drug delivery systems
3. Feedback-regulated drug delivery systems
4. Site-targeting drug delivery systems

Out of these classes first class contains new drug delivery systems as transdermal delivery, intra uterine delivery, ocular inserts, and sub dermal implants. The transdermal drug delivery has advantage to deliver medicines via skin to systemic circulation at a predetermined rate and maintain therapeutic concentration for prolong period of time.

1.1.2 Transdermal drug delivery system[3]

The idea of delivering drugs through skin is old, as the use is reported in 16th century in which the

husk of castor oil plant in water was placed on an aching head.

Today the transdermal drug delivery is well accepted for delivering drug to systemic circulation. Until recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven effective delivered through the skin typically cardiac drugs such as nitroglycerin and hormones such as estrogen.

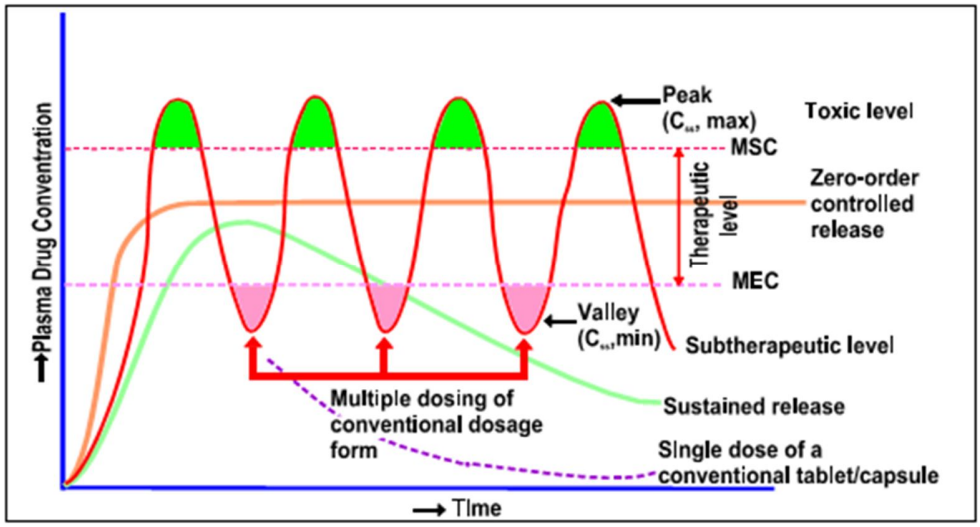


Fig 1: Comparative graphs of conventional, sustained and controlled release delivery systems

Non-medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists of two major sub-categories: therapeutic and cosmetic), aroma patches, weight loss patches and patches that measure sunlight exposure.

1.1.2.5 Fundamentals of Skin Permeation[10]

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.

A. Stratum Corneum as Skin Permeation Barrier

The average human skin contains 40-70 hair follicles and 200-250 sweat ducts per square centimeter. Especially water-soluble substances pass faster through these ducts; still these ducts don't contribute much for skin permeation. Therefore most neutral molecules pass through stratum corneum by passive diffusion. Thus, the stratum corneum acts as a passive, but not inert, diffusion medium (**Fig. 3**).

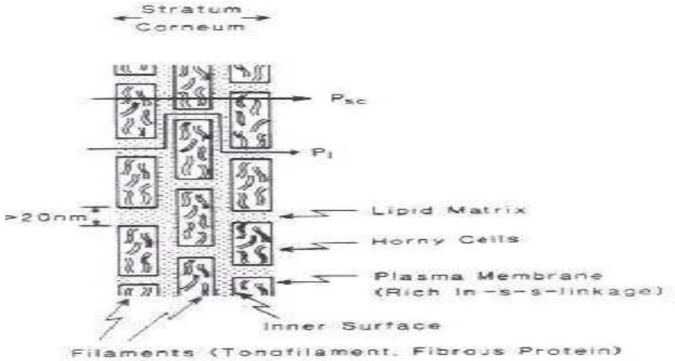


Fig 3: The Microstructure of Stratum Corneum

Series of steps in sequence:

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

The molecule is taken up into the microcirculation for systemic distribution (Fig. 4).

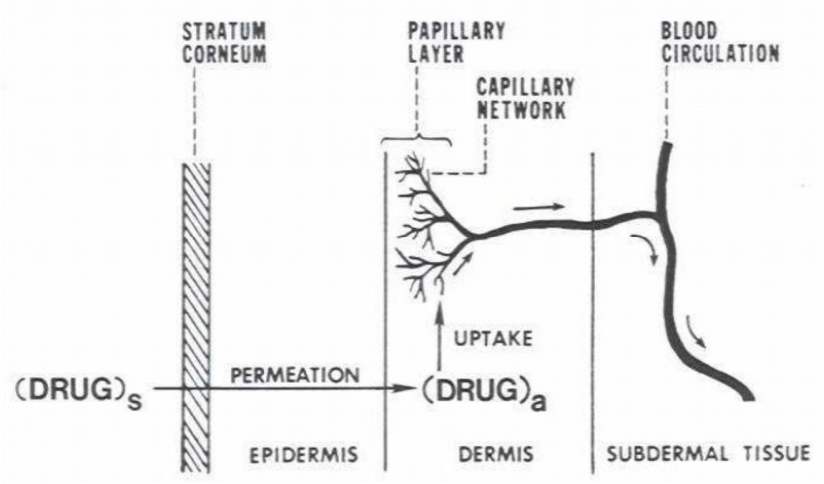


Fig 4: A multilayer skin model showing sequence of transdermal permeation of drug for systemic delivery

Table 1: Regional variation in Water Permeability of Stratum Corneum

Sr. no.	Skin region	Thickness (µm)	Permeation ($mg/cm^2/hr$)	Diffusivity ($cm^2/sec \times 10^{10}$)
1	Abdomen	15	0.34	6
2	Volar forearm	16	0.31	5.9
3	Back	10.5	0.29	3.5
4	Forehead	13	0.85	12.9
5	Scrotum	5	1.70	7.4
6	Back of hand	49	0.56	32.3
7	Palm	400	1.14	535
8	Plantar	600	3.90	930

B. Permeation pathways[2, 5]

Percutaneous absorption involves passive diffusion of the substances through the skin. A molecule may use two diffusional routes to penetrate normal intact skin, the appendageal route and the epidermal route (**Fig. 5**).

I. Appendageal route

Appendageal route comprises transport via sweat glands and hair follicles with their associated sebaceous glands (shown as no.1 & 3 in **Fig. 5**). These routes circumvent penetration through the stratum corneum and are therefore known as "shunt" routes. This route is considered to be of minor importance because of its relatively small area, approximately 0.1 % of the total skin area.

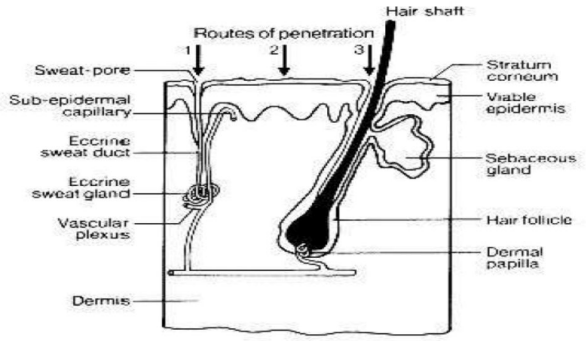
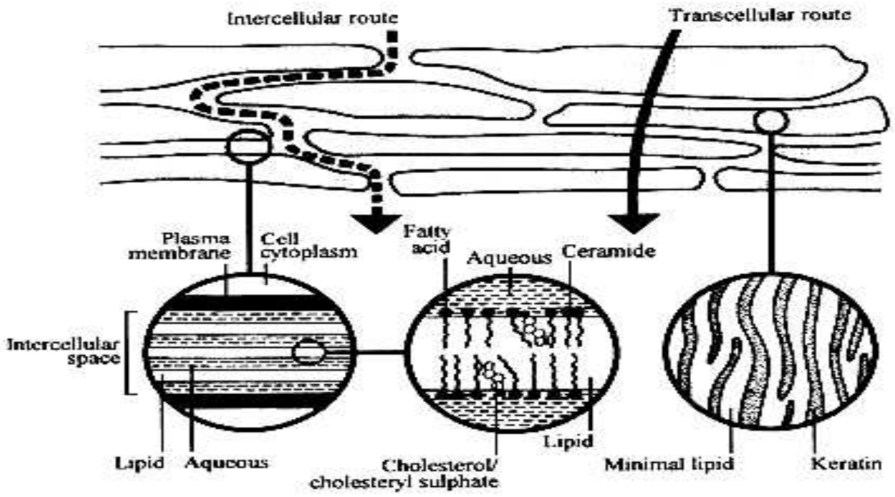


Fig 5: Routes for drug permeation

II. Epidermal route

For drugs, which mainly cross-intact horny layer, two potential micro routes exists, the transcellular (intracellular) and intercellular pathways (Fig. 6).



s Epidermal routes for drug permeation

1.1.2.7 Ideal molecular properties for transdermal delivery[5,7]

Ideal molecular properties for drug penetration are as follows:

- The partition co-efficient will be high if the molecular weight is less than 600 Daltons.
- An adequate solubility in lipid and water is necessary for better penetration of drug (log P: 1-3).
- Drug candidate must be non-ionic.
- Optimum partition co-efficient is required for good therapeutic action.
- Low melting point of drug is desired (<200°C).
- The pH of the saturated solution should be in between 5 to 9.
- The potent drug with dose of 10-15 mg/day is desired.

1.2. Technology for developing transdermal drug delivery systems[2,10]

The technologies can be classified in four basic approaches.

A. Polymer membrane partition-controlled TDDS

In this type of systems, the drug reservoir is sandwiched between a drug impermeable backing laminate and a rate controlling polymeric membrane (**Fig.7**).

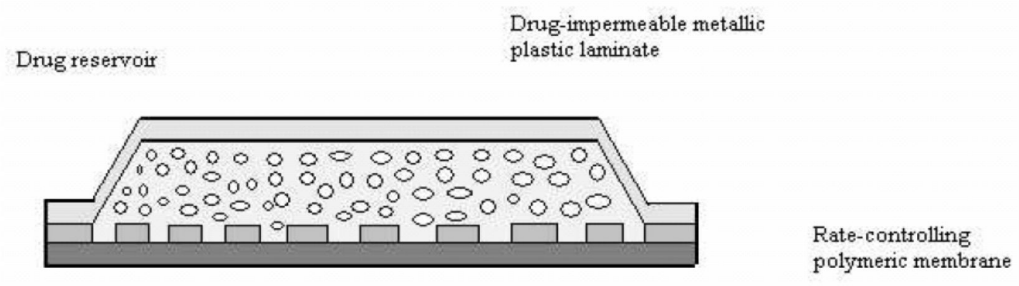


Fig 7: Cross-sectional view of polymer membrane permeation-controlled TDDS.

The drug is allowed to permeate only through the rate controlling membrane. The drug solids are homogeneously dispersed in a solid polymer matrix, suspended in an unleachable, viscous

liquid medium e.g. silicone fluid, to form a paste like suspension, or dissolved in a releasable solvent e.g. alkyl alcohol, to form a clear drug solution. The rate controlling membrane can be either a micro porous or a nonporous polymeric membrane e.g. ethylene-vinyl acetate copolymer, with specific drug permeability. On the external surface of the polymeric membrane a thin layer of drug compatible, hypoallergenic pressure sensitive adhesive polymer e.g. silicone adhesive, may be applied to provide intimate contact of TDDS with the skin surface. Varying the composition of drug reservoir formulation and the permeability co-efficient and thickness of rate controlling membrane can alter the drug release rate.

E.g. Some FDA approved systems –Transderm-Nitro for angina pectoris, Transderm-Scop for motion sickness, Catapres-TTS system for hypertension.

The intrinsic rate of drug release from this type of TDDS is defined by:

$$\frac{dQ}{dt} = \left(\frac{K_{m/r} K_{a/m} D_a D_m}{K_{m/r} D_m h_a + K_{a/m} D_a h_m} \right) C_R$$

Where, C_R is drug concentration in reservoir compartment
$K_{m/r}$ is the partition co-efficient for the interfacial partitioning of drug from the reservoir to the membrane
$K_{a/m}$ is the partition co-efficient for the interfacial partitioning of drug from membrane to adhesive
D_a is diffusion co-efficient in rate controlling membrane
D_m is diffusion co-efficient in adhesive layer
h_a is thickness of rate controlling membrane
h_m is thickness of adhesive layer.

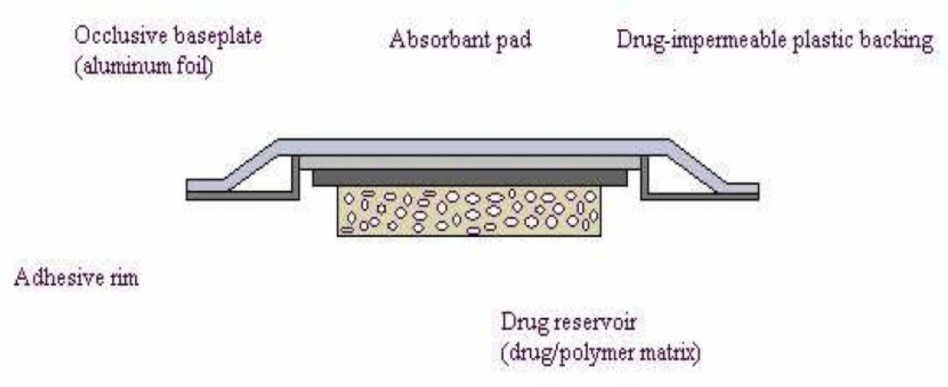


Fig 8: Cross-sectional view of polymer matrix diffusion-controlled TDDS

B. Polymer Matrix Diffusion-Controlled TDDS

In this system, the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix and then the medicated polymer formed is molded into medicated disks with defined surface area and thickness. This drug reservoir containing polymer disk is then mounted on occlusive base plate in a compartment fabricated from a drug-impermeable plastic backing. Instead of coating adhesive polymer directly on the surface of medicated disk, it is applied along the circumference of the patch to form a strip of adhesive rim surrounding the medicated disk (**Fig. 8**).

E.g. Nitro-Dur system and NTS system for angina pectoris.

The rate of release from polymer matrix drug dispersion-type is

$$\frac{dQ}{dt} = \left(\frac{L_d C_P D_P}{2t} \right)^{1/2}$$

Where, L_d is drug loading dose initially dispersed in polymer matrix
C_P is solubility of drug in polymer matrix
D_P is diffusivity of drug in polymer matrix

Alternately, the polymer matrix drug dispersion-type TDDS can be fabricated by directly dispersing drug in a pressure-sensitive adhesive polymer, e.g. polyacrylate, and then coating the drug-dispersed adhesive polymer by solvent casting or hot melt onto a flat sheet of a drug-

impermeable backing laminate to form a single layer of drug reservoir this yields a thinner patch.
E.g. Minitran system, Nitro-Dur II system for angina pectoris

C. Drug Reservoir Gradient-Controlled TDDS

Polymer matrix drug dispersion-type TDDS can be modified to have the drug loading level varied in an incremental manner, forming a gradient of drug reservoir along the diffusional path across the multi laminate adhesive layers (**Fig. 9**). The drug release from this type of drug reservoir gradient- controlled TDDS can be expressed by:

$$\frac{dQ}{dt} = \left[\frac{KF_{a/r}\,D_a}{h_a\,(t)}\right] L_d\,(h_a)$$

In this system, the thickness of diffusional path through which drug molecules diffuse increases with time, i.e. h_a (t). The drug loading level in the multi laminate adhesive layer is designed to increase proportionally i.e. L_d (h_a) so as to compensate time dependent increase n diffusional path as a result of drug depletion due to release.
Thus, theoretically this should increase a more constant drug release profile.
E.g. Deponit system containing nitroglycerine for angina pectoris

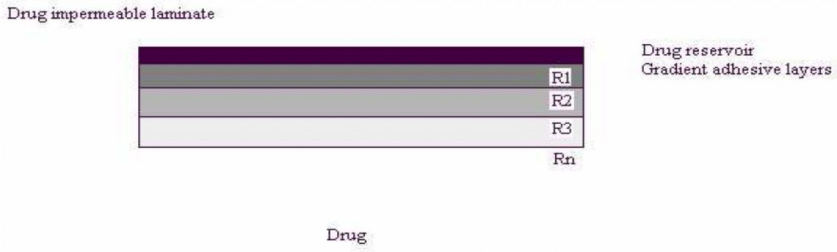


Fig 9: Cross-sectional view of a drug reservoir gradient-controlled TDDS

D. Microreservoir Dissolution-Controlled TDDS

A hybrid of reservoir and matrix dispersion type drug delivery systems which contains dug reservoir formed by first suspending the drug solids in an aqueous solution of water-miscible drug solubilizer e.g. propylene glycol then homogeneously dispersing the drug suspension with controlled aqueous solubility in a lipophilic polymer by high shear mechanical force to form thousands of unleachable microscopic drug reservoirs (**Fig. 10**).

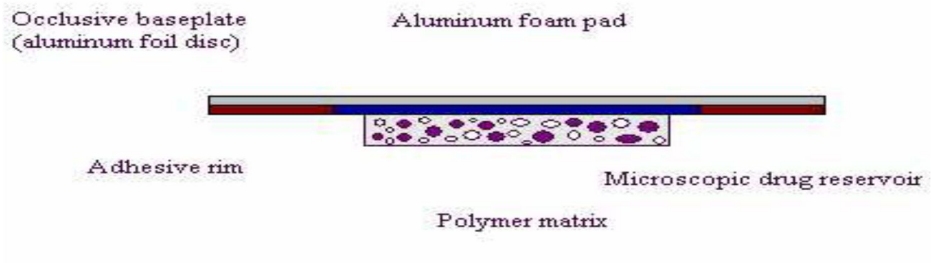


Fig 10: Cross-Sectional View of o Drug Microreservoir Dissolution-Controlled TDDS

E.g. Nitrodisk system for angina pectoris
The rate of drug release from this system is defined by:

$$\frac{dQ}{dt} = \frac{D_p D_1 A K_p}{D_p h_d + D_1 h_p A K_p}\left(B S_p - \frac{KF_{a/r} D_1 S_1 (1-B)}{h_1}\right)\left[\frac{1}{K_1} - \frac{1}{K_m}\right]$$

1.2.1 Types of TDDS[12-16]

a) Single layer drug in adhesive

In this type, the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and also responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

b) Multi layer drug in adhesive

This type is also similar to the single layer but it contains a immediate drug release layer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.

c) Vapour patch

In this type of patch, the role of adhesive layer not only serves to adhere the various layers together but also serves as release vapour. The vapour patches are new to the market, commonly used for releasing of essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

d) Reservoir System

In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane which can be micro porous or non porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug.

e) Matrix system

i. Drug-in-adhesive system

In this type, the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting (in the case of hot-melt adhesives) on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

ii. Matrix-dispersion system

In this type, the drug is dispersed homogenously 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.

f) Micro Reservoir System

In this type, the drug delivery system is a combination of reservoir and matrix-dispersion system. The drug reservoir is formed by first 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. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents.

1.2.3 Various methods for preparation of TDDS

A) Asymmetric TPX membrane method[17]

A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane and sealed by an adhesive.

- **Asymmetric TPX membrane preparation:** These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and non-solvent additives at 60°C to form a polymer solution. The polymer solution is kept at 40°C for 24 hr and cast on a glass plate to a pre-determined thickness with a gardner knife. After that the 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 min of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hr.

B) Circular Teflon mould method[18]

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same

organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butyl phthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hr 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 hr. The dried films are to be stored for another 24 hr at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. These type of films are to be evaluated within one week of their preparation.

C) Mercury substrate method[19]

In this method, drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 min to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation.

D) By using "IPM membranes" method[20]

In this method, drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 hr in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.

E) By using "EVAC membranes" method[21]

In order to prepare the 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 not soluble in water, propylene glycol is used for the preparation of gel. 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.

F) Aluminium backed adhesive film method[22]

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custammade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

G) Preparation of TDDS by using Proliposomes[23,24]

The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference, drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70°C temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 min. 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 desiccators 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.

H) By using free film method[25]

Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a

concentration of 40% w/w of polymer weight. 5 ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petridish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petridish. 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 desiccators until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.

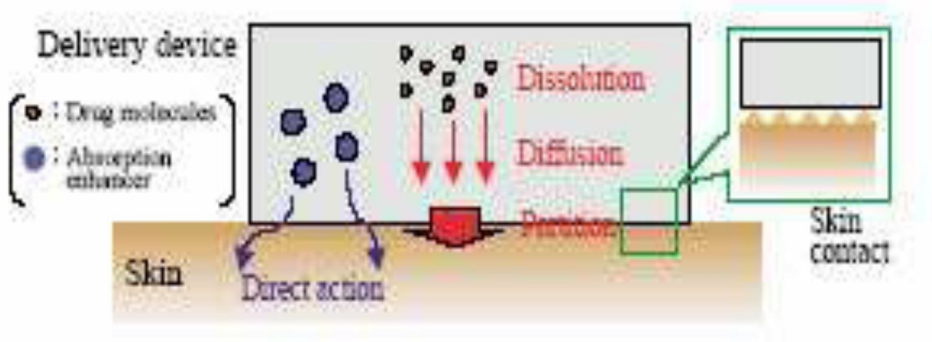


Fig 11: Action of Penetration Enhancers

1.2.3 Penetration Enhancers[4,5]

A) Chemical Enhancer

Incorporation of chemical enhancer facilitates the absorption of drug by altering the barrier property of the stratum corneum. A permeation enhancer should be pharmacologically inert, nontoxic nonirritant, non allergic, odorless, tasteless, colorless, compatible with most drug and excipient, inexpensive and good solvent property[26]. Different classes of penetration enhancers include alcohol, polyols (ethanol, propylene glycol), surfactants (tween, span, SLS), fatty acids (oleic acid), amines and amides (azone, N-methyl pyrrolidone), terpenes (limonene), sulfoxide (dimethyl sulfoxide), esters (isopropyl myristate) were developed over past two decades[27,28]. Permeation enhancers can enhance the skin permeability by a variety of mechanism, including interaction with intercellular lipid leading to disruption of their organization and increasing their fluidity[29], extraction of lipid from the stratum corneum, displacement of bound water, loosing of horny cells, delamination of stratum corneum[30], enhancing solubility and increasing partitioning into stratum corneum, interaction with intercellular proteins and keratin denaturation[31].

B) Mechanical / Physical approach

a. Iontophoresis

This method involves the application of a low level electric current either directly to the skin or indirectly via the dosage form in order to enhance permeation of a topically applied therapeutic agent[32-35]. Increased drug permeation as a result of this methodology can be attributed to either one or a combination of the following mechanisms: Electro-repulsion (for charged solutes), electro-osmosis (for uncharged solutes) and electro-pertubation (for both charged and uncharged).

b. Electroporation

This method involves the application of high voltage pulses to the skin that has been suggested to induce the formation of transient pores. High voltages (100 V) and short treatment durations (millisec) are most frequently employed. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e. small molecules, proteins, peptides and oligonucleotides) including biopharmaceuticals with molecular weights greater that 7 kDalton.

c. Microneedle-based devices[36]

The very first microneedle systems, described in 1976, consists of a drug reservoir and a plurality of projections (microneedles 50 to 100 mm long) extending from the reservoir, which penetrated

the stratum corneum and epidermis to deliver the drug.

d. Skin abrasion

The abrasion technique involves the direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medicaments. Some of these devices are based on techniques employed by dermatologists for superficial skin resurfacing (e.g. microdermabrasion) which are used in the treatment of acne, scars, hyperpigmentaion and other skin blemishes.

e. Needle-less injection

Transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin using a suitable energy source. The mechanism involves forcing compressed gas (helium) through the nozzle, with the resultant drug particles entrained within the jet flow reportedly traveling at sufficient velocity for skin penetration.

f. Ultrasound (sonophoresis and phonophoresis)[37]

This technique involves the use of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or via pre-treatment. It uses low frequency ultrasound (55 kHz) for an average duration of 15 sec to enhance skin permeability.

g. Laser radiation[38]

This method involves direct and controlled exposure of a laser to the skin that results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs.

h. Heat[39]

Heat enhance the skin permeation of drug by increasing body fluid circulation, blood vessel wall permeability, rate limiting membrane permeability and drug solubility thus facilitating drug transfer to the systemic circulation. When heat is applied, the kinetic energy of drug molecule, protein, lipid and carbohydrate is known to increase in the cell membrane. Also, the solubility of drug both in patch and within skin may increase with a rise in temperature. The effect of temperature on *in vivo* transdermal fentanyl flux was estimated at temperature of 32^0C and 37^0C. Drug flux approximately doubled over this 5^0C range. Heat may also cause change in physicochemical property of patches, sweating and increases hydration of skin, thus increasing permeation of drugs.

i. Magnetophoresis[27,40]

The term Magnetophoresis was used to indicate application of magnetic field and act as an external driving force to enhance drug delivery across the skin. It induce alteration in skin structure that could contribute to an increase in permeability. Magnetoliposomes consist of magnetic nanoparticles wrapped by a phospholipid bilayer which can be successfully applied for drug delivery system, magnetic resonance imaging markers for cancer diagnosis and thermal cancer therapy.

1.2.4 General clinical considerations in the use of TDDS[4]

The patient should be advised of the following general guidelines. The patient should be advised of the importance of using the recommended site and rotating locations within the site. Rotating locations is important to allow the skin to regain its normal permeability and to prevent skin irritation.

- TDDSs should be applied to clean, dry skin relatively free of hair and not oily, inflamed, irritated, broken or callused. Oily skin can impair the adhesion of patch. If hair is present at the site, it should be carefully cut, not wet shaved, nor should a depilatory agent be used, since later can remove stratum corneum and affect the rate and extent of drug permeation.
- Use of skin lotion should be avoided at the application site because lotions affect

the hydration of skin and can alter partition co-efficient of drug.
- Cutting should not physically alter TDDS, since this destroys integrity of the system.
- The protecting backing should be removed with care not to touch fingertips. The TDDS should be pressed firmly against skin site with the heel of hand for about 10 sec.

1.2.5 Evaluation parameters

- **Interaction studies**[41,42]
- 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. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.
- **Thickness of the patch**[43]
  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.
- **Weight uniformity**[43]
  The prepared patches are to be dried at 60°C for 4 hr 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.
- **Folding endurance**[43]
  A strip of specific area 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.
- **Percentage moisture content**[43]
  The prepared films are to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hr. After 24 hr the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

  Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100
- **Percentage moisture uptake**[43]
  The weighed films are to be kept in desiccators at room temperature for 24 hr containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hr the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.

  Percentage moisture uptake = [Final weight- Initial weight/ Initial weight] ×100.
- **Water vapour permeability (WVP) evaluation**[44]
  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

  $WVP=W/A$

  Where, WVP is expressed in gm/m^2 per 24 hr
  W is the amount of vapour permeated through the patch in gm/24hr
  A is the surface area of the exposure samples expressed in m^2.
- **Drug content**[44]
  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 analyze the drug content with the suitable method (UV or HPLC technique).

Each value represents average of three different samples.

- **Uniformity of dosage unit test**[45]
  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 hr and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2µm membrane filter and analyzed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated.
- **Polariscope examination**[45]
  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.

- **Shear adhesion test**[45]
  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 cross linking, 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. Shear adhesion strength is determined 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.

- **Peel adhesion test**[45]
  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 determine 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.

- **Thumb tack test**[45]
  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.
- **Flatness test**[42]
  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.
- **Percentage elongation break test**[46]
  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.

$$\text{Elongation percentage} = [(L1-L_2)/L_2] \times 100$$

Where, L_1 is the final length of each strip
L_2 is the initial length of each strip.

- **Rolling ball tack test**[46]
  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.

- **Quick stick (peel-tack) test**[46]
  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.

- **Probe tack test**[46]
  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.

- ***In vitro* drug release studies**[42]
  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 is then placed in a 500ml of the dissolution medium or phosphate buffer (pH 7.4) and the apparatus is equilibrated to 32± 0.5°C. The paddle is then set at a distance of 2.5 cm from the glass plate and operates at a speed of 50 rpm. Samples (5 ml aliquots) can be withdrawn at appropriate time intervals up to 24 hr and analyze by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

- ***In vitro* skin permeation studies**[42]
  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 is used. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin is thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrate for an hr in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and is placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell is 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 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 HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg/cm^2) vs. time in hr and permeability co-efficients are deduced by dividing the flux by the initial drug load (mg/cm^2).

- **Skin irritation study**[45]
  Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface ($50cm^2$) 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.

- **Stability studies**[42]
  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 are withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.

1.2.6 Marketed formulation[47]

Table 2: Examples of marketed transdermal drug delivery system

Product name	Drug	Manufacturer	Indication
Alora	Estradiol	Thera Tech/proctol & Gamble	Postmenstrual syndrome
Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism (males)
Catapres-TTS	Clonidine	Alza/Boehinger Ingelheim	Hypertension
Climaderm	Estradiol	Ethical Holdings/Wyeth-Ayerest	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals/Berlex Labs	Postmenstrual syndrome
CombiPatch	Estradiol/Norethindrone	Noven , Inc./Aventis	Hormone replacement therapy
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Duragesic	Fentanyl	Alza/Janssen Pharmaceutica	Pharmaceutical moderate/severe pain
Estraderm	Estradiol	Alza/Norvatis .	Postmenstrual syndrome
Fematrix	Estrogen	Ethical Holdings/Solvay Healthcare Ltd.	Postmenstrual syndrome
FemPatch	Estradiol	Parke-Davis	Postmenstrual syndrome
Habitraol	Nicotine	Novartis	Smoking cessation
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Nicoderm	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
Nicotrol	Nicotine	Cygnus Inc./McNeil Consumer Products, Ltd.	Smoking cessation
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Nitrodur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
Nuvelle	Estrogen/Progesterone	TS Ethical Holdings/Schering	Hormone replacement therapy
Ortho-Evra	Norelgestromin/estradiol	Ortho-McNeil Pharmaceuticals	Birth control

1.3 Drug and Excipient
Materials used in the present investigation

Table 3: List of materials used

Sr. No	Materials	Purpose
1	Anti diabetic drug	API
2	Eudragit NE 30D	Polymer
3	PVP K-30	Polymer
4	Triethyl citrate	Plasticizer
5	Dimethyl sulfoxide	Permeation enhancer
6	Acetone	Solvent
7	Sodium dihydrogen phosphate dihydrate	Buffer
8	Sodium hydroxide	pH adjustment
9	Sodium lauryl sulphate	Solubilizer

Purified water (from Milli-Q) was used in all the experiments, while R.O. water was used for the *in vitro* dissolution study.

1.4 Equipments used in the present investigation

Table 4: List of equipments used

Sr. No	Equipments	Make	Model
1	U.V Spectrophotometer-1800	Shimadzu, Japan	1800
2	Digital pH meter	Microtoniks	M-19
3	Melting point apparatus	Macro Scientific Works	403
4	Digital weighing balance	Mettler Toledo	JB2002
5	Mechanical stirrer	MB instruments	MB 575
6	Brookfield texture analyzer	Brookfield Engineering Labs, USA	CT3
7	Dissolution tester	Electrolab, Mumbai	TDT-06P
8	FTIR	Shimadzu, Japan	8400-S
9	Micrometer	Chem Instruments	MI-1000
10	Hot air oven	Digisystem Laboratory Instruments	DSO-300D

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