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Review Article

TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Delivery of drugs through the skin has been always a challenging area for research due to barrier properties exhibit by the outermost layer of skin stratum corneum. In the last two decades, the transdermal drug delivery system has become a proven technology that offers significant clinical benefits over other dosage forms. Because transdermal drug delivery offers controlled as well as predetermined rate of release of the drug into the patient, it able to maintain steady state blood concentration. It's a desirable form of drug delivery because of the obvious advantages e.g.convenient and pain-free self-administration for patients, avoidance of hepatic first-pass metabolism and the GI tract for poorly bioavailable drugs over other routes of delivery. The outlook for continued growth of the TDD market is very optimistic.Transdermal drug delivery has made an important contribution to medical practice, but has yet to fully achieve its potential as an alternative to oral delivery and hypodermic injections. This review emphasizes the three generations of transdermal drug delivery which start a new era of delivery of drug.

Keywords: Barrier, TDD, first pass metabolism.

INTRODUCTION

Since the beginning of life on the earth, humans have applied a lot of substances to their skin as cosmetics and therapeutic agents. However, it was the twentieth century when the skin became used as route for long term drug delivery.Today about two third of drugs (available in market) are taken orally, but these are not as effective as required. To improve upon the features the transdermal drug delivery system was emerged.Amongst all techniques which were used for release drugs in a controlled way into the human body, transdermal drug delivery system (TDDS) is widely recognized as one of the most reliable, appealing as well as effective technique.Delivery of drugs through the skin has been an attractive as well as a challenging area for research. Over the last two decades, transdermal drug delivery had become an appealing and patience acceptance technology as it is minimize and avoids the limitations allied with conventional as well as parenteral route of drug administration such as peak and valley phenomenon i.e. exhibit fluctuation in plasma drug concentration level, pain and inconvenience of injections; and the limited controlled release options of both.

***DEFINITION*:** [1,2,6,8,9,11,21,28]

A transdermal patch is defined as medicated adhesive patch which is placed above the skin to deliver a specific dose of medication through the skin with a predetermined rate of release to reach into the bloodstream.

Today the most common transdermal system present in the market mainly based on semipermeable membranes which were called as patches.

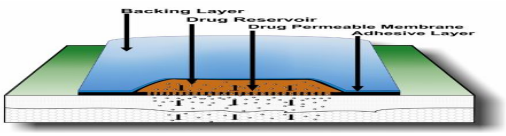

Fig.1.Transdermal patch showing its different components

TYPES OF TRANSDERMAL PATCHES: [12,15]

- **Single-layer drug-in-adhesive:**

In this system drug and excipients is inclusive with skin adhesive which serve as formulation foundation as a single breaking layer. The rate of release of drug through diffusion phenomenon.

Fig.2. Single layer drug in adhesive patch and its different component[12,15]

The rate of release of drug is expressed as :

$$\frac{dQ}{dT} = \frac{Cr}{\frac{1}{Pm} + \frac{1}{Pa}}$$

Where Cr = drug concentration in reservoir compartment;

Pa = Permeability coefficient of adhesive layer;

Pm = Permeability coefficient of rate controlling membrane

- **Multi-layer drug-in-adhesive:**

In this system drug and excipients incorporated with adhesive but both layer of adhesive separated by single layer membrane. The released of drug occurred through diffusion phenomenon.

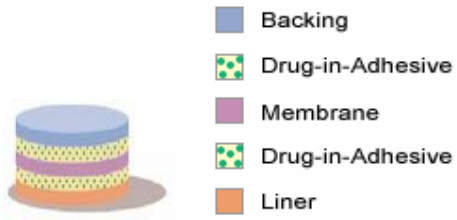

Fig.3.Multi layer drug in adhesive patch and its different component[12,15]

The rate of release of drug is governed by following equation:

$$\frac{dQ}{dT} = \frac{\frac{Ka}{r}.Da}{ha}Cr$$

Where Ka/r = partition coefficient for theinterfacial partitioning of the drug from the reservoirlayer to adhesive layer.

- **Drug reservoir-in-adhesive:**

In the reservoir system,inclusion of liquid compartment containing drug solution/suspension between baking layer and semipermeable membrane followed by adhesive layer and release liner.

Fig.4. Drug reservoir in adhesive patch and its different component[12,15]

The rate of drug release from this drug reservoir system is given by

$$\frac{dQ}{dT} = \frac{\frac{Ka}{r}.Da}{ha(t)}A(ha)$$

Where ha = thickness of adhesive layer; A = thickness of diffusional path

- **Drug matrix-in-adhesive**:

This system is designed by inclusion of semisolid matrix having drug in solution or suspension form which is in direct contact with the release liner.

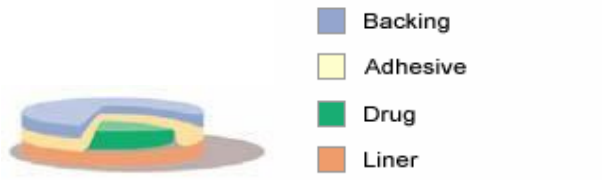

Fig.5. Single layer drug in adhesive patch with its different component[12,15]

The rate of release of drug is goverened by following equation:

$$\frac{dQ}{dT} = \frac{ACpDp^{\frac{1}{2}}}{2t}$$

Where A = the initial drug loading dose dispersed in the polymer matrix; C_p = solubility of the drug; D = diffusivity of the drug in the polymer

SKIN AS A SITE FOR DRUG INFUSION:[3, 8, 9, 12, 13, 14, 16]

The skin is the largest organ of the body. The skin an average adult body is about 20 square feet and it received about one third of total available blood. The skin is multi-layered organ composed of three histological tissue:

- the outermost layer of skin,epidermis is which provides a waterproof barrier and creates our skin tone.
- dermis, beneath epidermis, contains tough connective tissue, hair follicles, and sweat glands and
- deeper subcutaneous tissue (hypodermis) is made of fat and connective tissue.

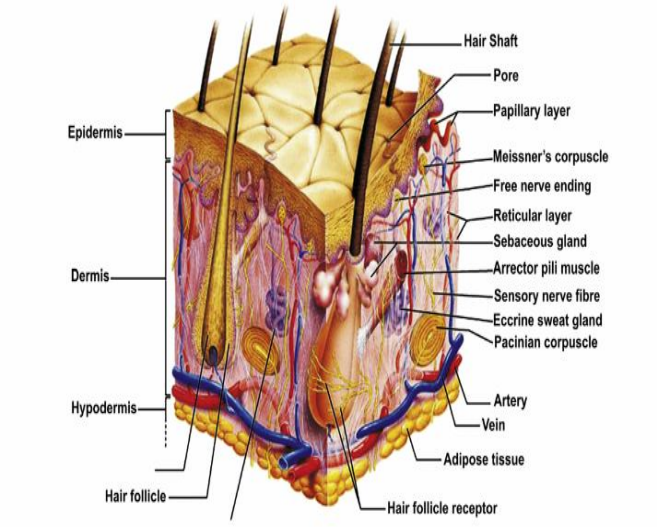

Fig.6. Anatomy of skin represents different parts[5]

There are main three pathways through which foreign particles diffused or penetrate in to skin:[5,16,19,28]

1. Transcellular/Intracellular permeation through the stratum corneum
2. Intercellular permeation through the stratum corneum
3. Transappendageal permeation via the hair follicles, sweat and sebaceous glan

Mechanism of transdermal permeation:[19,28]

Transdermal permeation of a drug moiety involves the following steps:

i. Sorption by stratum corneum
ii. Permeation of drug through viable epidermis
iii. Uptake of the drug moiety by the capillary network in the dermal papillary layer.
iv. The drug must possess some physicochemical properties to reach target site via systemically through stratum corneum. The rate of permeation of drug moiety across the skin is governed by following equation:

$$\frac{dQ}{dT} = P_s(C_d - Cr)$$

Where, C_d= concentration of penetrate in the donor phase (on the surface of skin); C_r= concentration of penetrate in the receptor phase(body); and $P_s$is the overall permeabilitycoefficient of the skin which is defined as

$$Ps = \frac{KsDss}{hs}$$

Where, K = Partition coefficient of the penetrant; D_{ss}= Apparent diffusivity of penetrant; h_s= Thickness of skin.

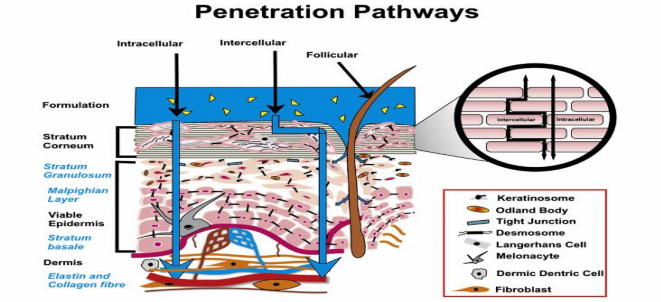

Fig.7. Different route of skin penetration[3]

A constant rate of drug permeation achieved, if $C_d > C_r$ then the equation reduced as:

$$dQ/dT = Ps.Cd$$

the rate of skin permeation (dQ/dt) becomes a constant, if the Cvalue remains fairly constantthroughout the course of skin permeation Tomaintain the $C_d$at a constant value, it is critical tomake the drug to be released at a rate (Rr) which is always greater than the rate of skin uptake (R_a), i. e., $R_r >> R_a$ as shown in figure.8.

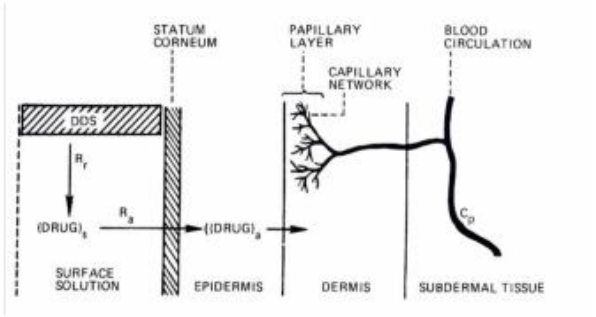

Fig.8. Schematic representation of the relationship between the rate of drug release (R_r) from a transdermal system and the rate of release of absorption (R_a) by the skin[12]

By doing so, the drug concentration on the skin surface (C_d) is maintained at a level which is always greater than the

equilibrium (or saturation) solubilityof the drug in the stratum corneum (C^e_s),i.e.,C_d>>C; and maximum rate of skin permeation$(dQ/dt)_m$ as expressed by equation

$$[dQ/dT]_m = P_s C_s^e$$

Apparently, the magnitude of $(dQ/dt)_m$is determinedby the skin permeability coefficient (P_s) of the drugand its equilibrium solubility in the stratum corneum(C^e_s).

Transdermal drug delivery systems have following benefits:[11,12,13,14,16,28]

1. Transdermal medication provides safe, convenient and pain-free self-administration for patients.
2. Transdermal delivery may be useful in those patients who are polymedicated.
3. Transdermal drug delivery provide a constant rate of release of medicine tomaintain concentration level of drug for a longer period of time as to avoid peak and valley associated with oral dosing and parenteral administration.
4. Transdermal patches improved therapeutic effect s of various drugs by avoiding specific problems associated with drugs such as presystemicmetabolism,formation of toxic metabolites, low absorption,gasto intestinal irritation etc.
5. Useful in drugs possesses short half-life as to avoid frequent dosing administration.
6. Reduced inter & intra – patient variability by simplified medication regimen.
7. Greater advantage in those patients who are unconscious, dysphagia or constipation.
8. Elimination of pre-systemic metabolismresult in reduction the amount of drug administered, resulting in the reduction of adverse effects and hence safer in hepato-compromised patients,
9. Fruitful in especially when long-term treatment is required, as in chronic pain treatment e.g. hormone replacement etc. and smoking cessation therapy.
10. The drug input can be terminated at any point of time by removing transdermal system.
11. Transdermal systems are generally inexpensive and economic when compared with other therapies on cost basis, as patches are designed to deliver drugs from 1 to 7 day.
12. The general acceptability of transdermal products by patients is very high, which is also proved from the increasing market for transdermal products.
13. Topical patches are easier to use and remember
14. Topical patches over an alternative to people who cannot, or prefer not to takemedications or supplements orally.
15. Provide relatively large area of application in comparison with the buccal or nasal cavity.

Limitations:[4,7,11,12,13,14,16]

1. The drug moiety must poessess some physicochemical properties for penetration through skin and if dose of drug is large i.e. more than 10-25mg/day transdermal delivery is very difficult. daily dose of drug preffered less than 5mg/day.
2. Local irritation at the site of administration such as itching ,erythema and local edema may be caused by drug or the excipients used in the formulations.
3. Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
4. Some patients develop contact dermatitis at the site of application due to system components.
5. The barrier function of the skin changes from one site to another ,from person to person and with age.
6. Poor skin permeability limits the number of drugs that can be delivered in this manner.
7. A high drug level cannot achieve by this system.
8. Transdermal drug delivery is unable to deliver ionic drugs.
9. Transdermal drug delivery system is restricted to potent drug.
10. It cannot deliver drugs in a pulsatile fashion.
11. Tolerance inducing drugs or those (e.g., hormones) requiring chronopharmacologicalmanagement is not suitable candidates.
12. Required significant lag time.
13. Drug molecule having large molecular size (>1000 Dalton) cannot developed for transdermal deliver.

Basic components of transdermal system:[5,8,10,11,12,16,25,28]

Polymer matrix or matrices: Polymers are the foundation of transdermal system. The selection of polymer and design are of prime importance.

Considerations for polymer selection in transdermal delivery system:

- Should be stable and non-reactive with the drug moiety.
- Easily available, fabricated and manufactured in to desired formulations.
- The properties of polymer e.g. molecular weight glass transtition temp. melting point and chemical functionality etc. should be such that drug can easily diffused through it and with other components of system.
- Mechanical properties should not change if large amount of drug incorporate.
- Should provide consistent release of drug throughout the life of system.

The polymers used in transdermal system are:

Natural Polymers: e.g. zein, gelatin cellulose derivatives, , , gums, natural rubber,shellac, waxes and chitosan *etc.*

Synthetic Elastomers: e.g., hydrin rubber, polyisobutylene, polybutadiene, silicon rubber, nitrile, , neoprene, butylrubber,acrylonitrile *etc*.

Synthetic Polymers: e.g. polyvinylchloride, polyethylene,polyvinyl alcohol, polypropylene, polyamide, polyacrylate, polyurea, polyvinylpyrrolidone,polymethylmethacrylate*etc.*

Polymers used in transdermal system in versatile manner such as:

- **Rate controlling membrane:** It control the release of drug by disperse through an inert polymer matrix. The polymer powder blended with drug moiety by physical manner and then moulded in to desired shape with required thickness and surface area.
- **Adhesive:** make an intimate contact between the skin and transdermal system. It carries the drug which is dissolved or dispersed in solution or suspension form. The quality of drug diffused in to skin depending on the holding power..
- **Pressure sensitive adhesive:** Hitherto the rapidity of transdermal system can be done by pressure sensitive adhesive. The three most commonly usedadhesives are polyisobutylene, polyacrylate and silicones in TDD devices.

Release liners: The patch is covered by protective liner during storage until it is used .The release liner removed and discarded just before the application of patch over the skin since release liner is in intimate contact with the transdermal system hence it should be physically as well as chemically inert. The release liner is composed of a 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. Other materials used as release liner in transdermal patches include polyester foil and metalized laminate.

Backing laminate: While design the baking layer following points must be in consideration:

- Must be flexible.
- Having low water vapour transmission rate so as to promote skin hydration and thus greater skin permeability of drug
- Should be compatible with transdermal system as remain in use while applying.
- Should be chemical resistance.
- Having good tensile strength.
- Non irritant

Examples of backings laminate are polyethylene film, polyester film, and polyolefin film, and aluminumvapor coated layer.

Drug: Transdermal delivery of drugs has taken a surge of popularity nowadays. Various physicochemical, pharmacokinetic and pharmacological properties of the drug should be considered for transdermal system development. Because of the limited permeability of the skin, drugs have to be transdermally delivered by passive diffusion through the skin, and are limited by several substantial constraints.

The drug moiety for transdermal system should be potent (dose in mg), having molecular weight ≤ 1000 Da, , adequate solubility in the vehicle, logP value of < 5, melting point of 200 °C and appropriate lipophilicity, undergo extensive presystemic metabolism, non-ionic and non-irritant areconsidered as suitable candidates for delivery via this route

Penetration enhancers: Compounds which promote the penetration of topically applied drugs are commonly referred as absorption promoters, accelerants, or

penetration enhancers. Penetration enhancers are incorporated into a formulation to improve the diffusivity and solubility of drugs through the skin that would reversibly reduce the barrier resistance of the skin. Thus allow the drug to penetrate to the viable tissues and enter the systemic circulation.

Desired properties for penetration enhancers:

i. It should be non-irritant, non-sensitizing, non-phototoxic, and non-comedogenic.
ii. Onset of action should be rapid and duration of activity should be predectible and reproducible.
iii. Have no pharmacological activity in the body i.e. should not bind to the receptor site.
iv. Upon removal of the enhancer, the upper layer should immediately and fully recover its normal barrier property.
v. The barrier function of the skin should reduce in one direction only .Endogenous material should not be lost to the environment by diffusion out of the skin.
vi. The accelerants should be chemically and physically compatible with all drugs and adjuvants to be formulated in topical preparations and devices.
vii. It should be inexpensive, tasteless and colourless,
viii. It should readily formulated in to dermatological preparations.
ix. It should have a desired solubility parameter that approximates that of skin.
x. It should adhere and spread well on the skin with a suitable skin feel.

Some of the examples of the widely used classical enhancers involve various classes that include water, hydrocarbons alcohols, acids amines, amides, esters, surfactant terpenes, terpenoidsand essential oil, sulfoxides, lipids and miscellaneous such as cyclodextrin derivatives, chitosan etc.

Other excipients:

Plasticizers: Palsticizers have also been used in many formulations ranging from 5 to 20% (w/w, dry basis). Along with the brittleness and ductility of the film, it is also responsible for adhesiveness of the film with other surfaces or membranes and improvement in strength of film. Some of its examples are glycerol or sorbitol, at 15%,w/w, dry basis, phosphate, phthalate esters, fatty acid esters and glycol derivatives such as PEG 200, and PEG 400.

Solvents: Various solvents such as methanol, chloroform, acetone, isopropanol and dichloromethane etc. are used to prepare drug reservoir.

Approaches in the development of transdermal therapeutic system:[5, 10, 11, 12, 13, 14, 16]

Several technologies have been successfully developed to provide a rate control over the release and the transdermal permeation of drugs. These technologies are as follows:

Adhesive dispersion type system:

The system consists of drug-impermeable backing membrane, the drug reservoir which is prepared by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting or hot melting onto a flat sheet of drug-impermeable backing to form a thin drug reservoir layer. On top of this, a layer of rate-controlling adhesive polymer(non-medicated) of constant thickness is spread to produce an adhesive diffusion-controlled drug delivery system with detachable release liner which in an ideal situation is removed and the patch is applied to the skin for a required period of time.

Illustration of this type of system is exemplied by development and marketing of transdermal therapeutic system of angina pectoris and Valsartan as angiotensin II type 1 selective blocker for one day medication.

Membrane permeation controlled system:

In this system the drug reservoir is totally embedded in a compartment molded between a drug-impermeable backing laminate and a rate controlling polymeric membrane The drug molecules are permitted to release across the rate controlling membrane simply by diffusion process through the pores. In the reservoir compartments the drug solids are dispersed homogenously in a solid polymeric matrix (e.g. polyisobutylene) suspended in the unleachable viscous liquid medium (e.g. silicon fluid) to form a gel-like suspension, or dissolved in a releasable solvent (e.g. alkyl alcohol) to form a gel like in solution. The rate controlling membrane, can be either a microporous or non-porous polymeric membrane e.g. ethylene–vinyl acetate copolymer, having specific drug permeability. On the top surface of the polymeric membrane a thin layer of drug compatible adhesive polymer, e.g., silicone adhesives, can be applied, to provide intimate contact of the transdermal system with the skin surface. The release rate from this transdermal system can

be tailored by varying the polymer composition, thickness of the rate controlling membrane , permeability coefficient and adhesive. Examples of this system are TransdermScop (Scopolamine- 3 days protection) of motion sickness and TransdermNitro (Nitroglycerine-for once a day)medication of angina pectoris

Matrix diffusion controlled system:

In this approach, the drug reservoirs are prepared by homogeneously dispersing drug particles in a hydrophilic or lipophilic polymer matrix or combination of both.. The resultant medicated polymer is then molded into a medicated disc with a defined surface area and controlled thickness. The dispersion of drug particles in polymer matrix can be accomplished by either homogenously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of the polymer chains or homogenously blending drug solids with a rubbery polymer at an elevated temperature and/or under vacuum. The polymer disc which contains drug reservoir is fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing. The adhesive polymer is then spread to form a strip of rim along the medicated disc. This matrix type of transdermal system is best exampled by the nitroglycerinreleasing transdermal therapeutic system. The advantage of matrix dispersion type transdermal systemis the absence of the dose dumping since the polymer cannot rupture.

Microreservoir type controlled system:

This system is basically hybrid of reservoir and matrix-dispersion type of drug delivery system.In this approach, drug reservoir is formed by suspending the drug in an aqueous solution of liquid polymer and then dispersing the drug suspension homogeneously in a lipophilic polymer e.g.silicone elastomers by high energy dispersion technique by shear mechanical force to form thousands of unreachable, and microscopic spheres of drug reservoirs. This technology has been utilized in the development of Nitro disc. Release of a drug from a micro reservoir-type system can follow either a partition-control or a matrix diffusion-control depending upon the relative magnitude of solubility of the drug in the liquid compartment and in the polymer matrix.

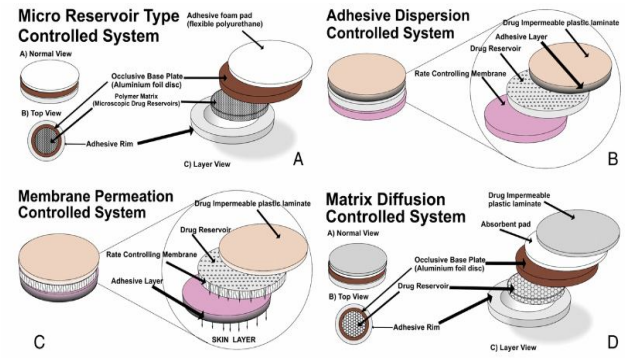

Fig.9.(A): Showing the presence of microscopic spheres of drug reservoir,(B) Development of adhesive dispersion controlled therapeutic system (C)Diagrammatic representation of membrane permeation controlled system, (D): Representation of matrix type transdermal system.[5]

Evaluation of Transdermal system:[8,10,11,12,13,14,15,16,28]

Interaction studies: The drug and polymer compatibility was characterized by means of FTIR spectroscopy. The compatibility was checked by making physical mixture of drug and polymer (1:1) and then the FTIR analysis of the mixture was done. The peaks should not be changed in FTIR spectra of mixtures, and it should be similar to the pure drug and polymer FTIR spectra.

Physical evaluation of transdermal system:

Film thickness: The thickness of film is measured by using micro meter, electronic vernier callipers, with a least count of 0.01mm, dial gauge, or screw gauge. Thickness is measured at five different points on the film and average of five readings is taken.

Percentage flatness: Film is cut in to strips, two from either end or one from the center. The length of these strips is measured to the nearest centimetre without applying any additional pressure. The percentage flatness of the strips is selected as the average per cent of length calculated from the 7 cm strips. Zero percent constriction is equivalent to 100 percent flatness.

% Constriction = $\frac{(Initial\ length - Final\ length)}{Initial\ length} X\ 100$

Folding endurance: folding endurance of patches can be determined by repeatedly folding a small strip of film (2 x 2 cm) at the same place till it breaks.The number of time the

film could be folded at the same place without breaking is the folding endurance value.

Tensile strength: The tensile strength can be determined by using a modified pulley system. weight is gradually increased so as to increase the pulling force till the patch breaks. The force required to break the film is considered as tensile strength and it is calculated as kg/cm².

$$Tensile\ Sterngth = Tensile\frac{Load}{Cross}\ section\ Area$$

Patch thickness: Patch thickness can be measured by using digital micrometer screw gauge at three different points and the mean value is calculated.

Elongation break test: The elongation break is to be determined by noting the length just before the break point. The elongation break can be determined by the formula:

$$\text{Elongation break} = \frac{(Final\ length - Initial\ length)}{Initial\ length}$$

Weight uniformity: weight uniformity is studied by randomly selected patches about 10 in number. A specified area of patch is to be cut in different parts of the patch and weighed in a digital balance. Calculate average weight and standard deviation value from the individual weights. Such determination is performed foe each formulation.

Drug content: A film of required area (1 x1 cm / 2 x 2 cm etc.) is cut,put this small piece of film in to 100 ml buffer (pH 7.4 or 6.8 or as prescribed) and shaken continuously for 24 hours. Then the whole solution is ultrasonicated for 15 minute. After filtration, the drug is estimated spectrophotometric ally and the drug content is determined.

Percentage of moisture content: The films are weight individually and left in a dessicator containing anhydrous calcium chloride or activated silica at room temperature for 24 hours. Individually films are weighed repeatedly until they showed a constant weight. Calculation of % of moisture content is done as the difference between initial and final weight with respect to the final weight.

$$\%\ moisture\ \text{Content} = \frac{InitialWeight - FinalWeight}{FinalWeight} \times 100$$

Percentage of moisture uptake: A weight film kept in a dessicator at room temperature for 24 hours is taken out and exposed to 84% relative humidity (a saturated solution of potassium chloride) in a dessicator until a constant weight for the film is obtained. The percentage of moisture uptake is calculated as the difference between the final and initial weight with respect to initial weight.

$$\%\ Moisture\ Uptake = \frac{(Final\ weight - Initial\ weight)}{Initial\ Weight} \times 100$$

Water vapour transmission rate: Glass vials approx. 5 ml capacity of equal diameter were taken for transmission study. All vials washed thoroughly and dried in an oven completely. Weigh about 1 gm of anhydrous/ fused calcium chloride and kept in respective vials. Fix the films on the brim of vials and weigh individually then kept in closed dessicator containing saturated solution of potassium chloride to maintain humidity approx. 84%. The vials were weighed in 6 , 12 , 24 ,36 , 48 , and 72 hours respectively.

$$Transmission\ rate = \frac{(Final\ Weight - Initial\ Weight)}{Area \times Time} \times 100$$

Content uniformity test: Select 10 patches but content is determined for individual patches. If 9 out of 10 showed content between 85-115% of the specified value and no one has shown 75-125% of the specified value,it means the test has been passed but if 3 patches shown the content between 75-125% then taken 20 additional patches and further test performed. If these 20 patches shown content between 85-115 % ,then the patches passed the test.

Uniformity of dosage unit test : A patch of accurately weigh is cutted in to small pieces and transferred to volumetric flash containing specific volume of suitable solvent for dissolution of drug and then sonicated for a limited period of time for complete extraction of drug from pieces and then mark the volume with the same solvent. The solution obtained kept untouched for 1 hour to settle down then supernatant diluted as required. The dilute solution was filtered by membrane having pore size 0.2µm and analyzed with suitable analytical (HPLC / UV) technique and the calculation was done for drug content.

Polariscope examination: The instrument polariscope used to study the crystal structure of drug in a patch. A specifiec area of patch is cut and kept on the slide to observe that drug present in crystalline form or amorphous form.

Adhesive studies:

Shear adhesion test: The cohesive strength of an adhesive polymer is determined by this test. The value of strength can be affected by the degree of cross linking, the molecular weight, the composition of polymer and the amount of tackifiers added. An adhesive coated patch is stacked on plate made of stainless steel and specified weight hung from the patch parallel to this plat . The time taken to pull off the patch from the plate determines the cohesive strength. More the time taken, greater is the shear strength.

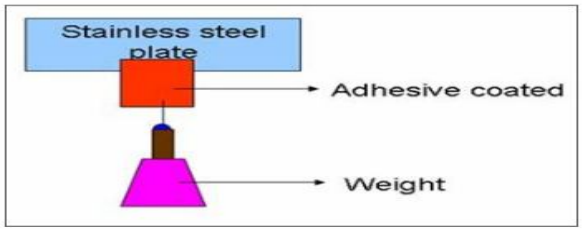

Fig.10. Shear strength test

Peel adhesion test: The measure of patch strength between an adhesive and a substrate is defined as adhesion. The force required removing adhesive coating from the steel used as test substrate. The type and amount of polymer tme molecular weight and the composition of polymers determine the adhesive properties. The single patch is adhere to test substrate (Steel) and it pulled from the substrate at 180^{o} angle. No residue on the test substrate indicate failure of adhesive

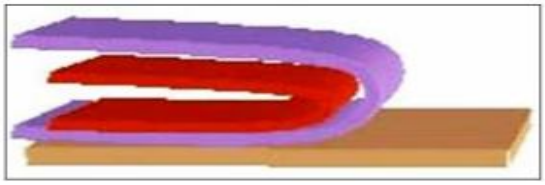

Fig.11. Peel adhesion test

Tack properties: Tack is the ability of polymer to adhere to a substrate with little fingure pressure It's important in transdermal systems which are applied with little figure pressure. Tack is dependent on molecular weight as well as composition of polymer and tackifying resins used in the polymer.

Tests for tack include:

Thumb tack test: This is subjective test in which evaluation is done by pressing the thumb in to the adhesive. Experience is required for using the test.

Rolling ball tack test: This test involves measurement of distance travelled by a stainless steel along the upward face of adhesive. The diameter of ball is 7/16^{o} inches and it released on inclined track having angle 22.5^{o}More the distance travelled, less the tacky polymer.Distance travelled by ball is measured in inches which determine the tackiness of polymer. It determines the softness of adhesive polymer.

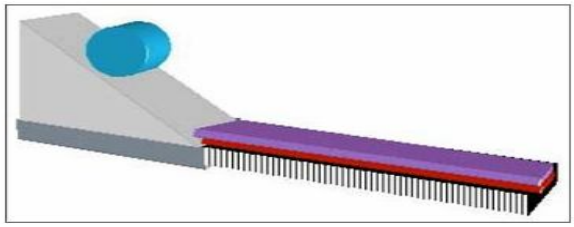

Fig.12. Rolling Ball Tack Test

Peel tack or quick stick test: The peel force is the force required to break the bond between the adhesive and the test substrate. The patch is pulled away from the substrate at 90^{o} with speed 12 inches/minute. The value of force is expressed in grams/inch or ounces/inch.

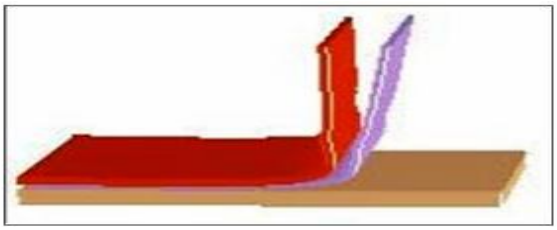

Fig.13. Peel tack test

Probe tack test : In this, the tip of probe with defined surface roughness brought in to contact with adhesive and when the bond is formed between the adhesive an probe, removal of probe at a fixed rate away from the adhesive which break the bond. The force required to break the bond is recorded as tack and it is expressed in grams.

Fig.14.Probe tack test

Skin irritancy studies: The skin irritancy can be performed on healthy rabbits / mice albino / rats and potential of transdermal system can be evaluated by modified Draize test. The dorsal surface of given test animal is to be cleaned and remove the hair from the clean surface then applied rectified sprit. Applied the transdermal formulation over the clean surface for 24 hour. After this period, remove the formulation and observed the status of skin.The score are given from 0 to 4 depending the degree of erythema as follows : zero point given for no erythema , 1 point for slight erythema-(barely perceptible-light pink), 2 poinst for moderate erythema(dark pink),3 points for moderate to severe erythema(dark pink) and 4 points for severe erythema (extreme redness).

Confocal laser scanning microscopy(clsm) : Depth of skin penetration of a patch can be assessed using CLSM. Transdermal formulation is applied non-occulsively for8 hours to the dorsal skin. The mice is sacrificed by heart puncture, dorsal skin is excised and washed with distilled water. The excised skin is then placed on aluminium foil and the dermal side of the skin is generally teased off any adhering fat and/ or subcutaneous tissue. These are then cut in to pieces of 1mm^2 and tested for probe penetration. The full skin thickness is optically scanned at different increments through the z-axis of a CLS microscope.

Stability studies: The stability of active component is a major criterion in determining acceptance or rejection of transdermal system. The stability studies were performed as according to ICH guidelines as at different temperature and relative humidity 25-30^oC (60% relative humidity) and 45-50^oC (75% relative humidity) over a period of 60 days. The sample were withdrawn at 0,3,6, and 9 weeks respectively and were analyazed for their physical appearance, drug content and in-vitro diffusion studies.

In-vitro release studies: The best available tool today which can at least quantitatively assure about the biological availability of a drug from its formulation is its in vitro dissolution test.

Paddle over dics apparatus (USP apparatus 5): this apparatus is quite similar to paddle apparatus (USP apparatus II) except that the patches were stick on a disc or holder placed at the bottom of apparatus and temperature of the medium maintained at 32 ± 0^oC.

Cylindrical apparatus (USP apparatus 6): This apparatus also used for evaluation of transdermal formulations and it is identical to rotating apparatus (USP apparatus 1) . In this apparatus, a stainless steel is used to hold the sample. The sample is placed on an inert porous cellulose material and adhered to the cylinder.

Reciprocating disc : In this apparatus, the sample are placed on disc shaped holders using inert porous cellulosic support which reciprocating vertically by means of drive inside a glass container containing dissolution medium. The test is performed at 32^oC and reciprocating frequency maintained at 30 cycles/min.

The samples were withdrawn at appropriate interval of time and equal amount of buffer is replaced by buffer. The samples were diluted suitably and absorbance determined spectrophotometrically.

***In-vitro* skin permeation and release kinetics studies:**

The design and development of transdermal patch is greatly influenced by in vitro studies. In-vitro studies greatly help in investigating the route of skin permeation and the rate of transfer through skin by which drug entered in to systemic circulation. These studies can easily performed and methodology used allowed flexibility in adapting the model in addressing different aspects involved in preliminary or feasibility studies in the development of transdermal patch.

Franz Diffusion Cell: The in-vitro skin permeation of transdermal patches can be studied using Franz diffusion cell(most commonly used) with an effective permeation area of 1.0cm^2 and receptor cell volume of 10 ml . The temperature is maintained at 32^oC ± 1^oC .The receptor compartment is filled with 10 ml PBS and is constantly stirred in a magnetic stirrer at 100rpm. The skin is mounted on a receptor compartment with the stratum corneum side facing upward in to the donor compartment. Samples are withdrawn through the sampling port of the diffusion cell at predetermined time interval over 24 hours and are analysed. The receptor phase is immediately replenished with equal volume of fresh diffusion buffer.

Horizontal-type skin permeation system: Next to the Franz diffusion cell, this is most commonly used for permeation study. In this both receptor and donor compartment has capacity of 3.5 ml of PBS and constantly rotated by matched set of star head magnets at 600rpm and membrane area is

about 0.64cm^2. The temperature is controlled by thermostat water through water jacket surrounding the both compartment.

Flow Diffusion Cell: This diffusion cells has the advantage that they can be used when the drug has lower solubility in the receptor compartment. This cell is fully automated and connected directly to HPLC. They have large capacity donor chamber to allow appropriate loading of the applied compound and a low volume (0.3ml) receiving chamber that ensures rapid removal of penetrant at relatively low pumping rates.

***IN-VIVO* STUDIES:** These studies are the true depiction of formulation performance. The variableswhich were not considered during in-vitro study taken in to account now.

In-vivo studies of transdermal system can be done by using following model

- Animal Models
- Human volunteers
- Biophysical Model

Animal Models: For in-vivo studies animals are generally preferred at small scale because of easily availability and economically view. In human, considerable time and resources are required for study. The animal species used in in-vivo study are: rat guinea pig, hairless mouse, hairless rat, hairless dog, cat horse, goat, rhesus monkey, miniature pig, squirrel, chimpanzee, etc. The most preferred animal used in in-vivo study is rhesus monkey.Various experiments have been carried out to determine which of the animal models provide the best prediction of the behaviour of the device, being tested, in humans.

Human volunteers: The ultimate stage during clinical phases in development of transdermal devices is collection of all pharmacokinetic and pharmacodynamic data from human volunteers which were required to evaluate any toxic effects generate during application of formulations. The determination of percutaneous absorption in human can be done by labelling of drug by C^{14} radioisotope and measuring the radioactivity in excreta but it required very attention as to know how much amount reside in body and how much excrete by other routes not defined. The method is give approx. absolute result however it has some limitations. To overcome these limitations, other methods developed which were defined as :

Reservoir Technique: In this study, short exposure of radiolabelled compound to skin followed by removal of upper layer of skin (stratum corneum) by tape strriping and analyse the content of compound in the stratum corneum. By this method it is helpful to determine the amount of drug penetrate over a long period of time.

Mass Balance Technique: In this technique, the application site is covered with an occlusive chamber and this chamber being replaced by a new one after a particular time period and washing is done at the time of replacing. Radio-labelled compound were used and the chambers, washings and the faces and urine of the patients were analysed subsequently. Advantage of this technique include achievement of mass balance between the applied dose and excretion levels and the use of surface wash measurements for predicting percutaneous absorption.

Biophysical Models: Also known as physiologically based pharmacokinetic models. These Models are based on known anatomical and physiological datas thus present an accurate picture of drug disposition in various organs and tissues. All these models were based on steady state mass balance equation, solution of fick's second law of diffusion.

Application of Transdermal Drug Delivery System:

- Nicotinetransdermal patch marketed as Nicodermis to help in smoking cessation. It is the highest selling patch in United State.
- Two opioid medicationsFentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans) used to provide round-the-clock relief for severe pain available in patch form:
- Estradiol patches available as Estraderm for treat menopausal symptoms as well as postmenopausal osteoporosis. It is also available in combination with levonorgestrel as Climara Pro for menopausal symptoms.
- Nitroglycerintramsdermal patches For the treatment of angina pectoris, prescribed in place of sublingual pills.
- Transdermal patch of clonidine available for treatment of hypertension.
- Transdermal patch of the selegiline(MAO inhibiter) became the first transdermal delivery agent for major depressive disorder.

- Transdermal delivery agent Methylphenidate for the Attention Deficit Hyperactivity Disorder (ADHD).

Transdermal Market Product :

An increasing number of TDD products continue to deliver real therapeuticbenefit to patients around the world.Over the past 5 years (2003–2007), that rate has more than tripled to a new transdermal delivery system every 8 months. It is assumed that more than one billion transdermal patches are currently producedevery year.

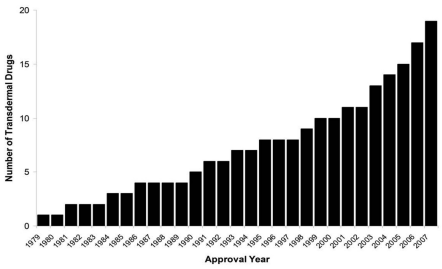

Fig.15. Graphical representation of transdermal drugs and their approval year

Advancement in Transdermal Drug Delivery:[6,9,13,15]

From a global view, advancement occur in transdermal delivery systems can be categorized in to three generations of development. In the first generation of systems that produced many of today's patches by judicious selection of drugs that can cross the skin at therapeutic rates with little or no enhancement; through the second generation that has yielded additional advances for small molecule delivery by increasing skin permeability and driving forces for transdermal transport; to the third generation that will enable transdermal delivery of small molecule drugs, macromolecules (including proteins and DNA) and virus-based/other vaccines through targeted permeabilization of the skin's stratum corneum.

First-generation transdermal delivery systems:

In almost all transdermal patch designs, the drug is stored in a reservoir which is enclosed on one side with an impermeable backing membrane and has an adhesive layer on other side that contacts the skin. Some designs involve drug dissolved in a liquid or gel-based reservoir, which permit the use of liquid chemical enhancers.

Table1: Transdermal drugs approved by the US FDA:

year	Drug	Indication	Product Name	Marketing company
1979	Scopolamine	Motion sickness	Transderm-Scop	Novartis Consumer Health (Parsippany, NJ)
1981	Nitroglycerin	Angina pectoris	Transderm-Nitro	Novartis (East Hannover, NJ)
1984	Clonidine	Hypertension	Catapres-TTS	BoehringerIngelheim (Ridgefield, CT)
1986	Estradiol	Menopausal symptoms	Estraderm	Novartis (East Hannover, NJ)
1990	Fentanyl	Chronic pain	Duragesic	Janssen Pharmaceutica (Titusville, NJ)
1991	Nicotine	Smoking cessation	Nicoderm, Habitrol, ProStep	GlaxoSmithKline (Philadelphia, PA), Novartis Consumer Health (Parsippany, NJ) Elan (Gainesville, GA)
1993	Testosterone	Testosterone deficiency	Testoderm	Alza, Mountain View, CA
1995	Lidocaine/epinephrine (iontophoresis)	Local dermal analgesia	Iontocaine	Iomed (Salt Lake City, UT)
1998	Estradiol/norethidrone	Menopausal symptoms	Combipatch	Novartis (East Hannover, NJ)
1999	Lidocaine	Post-herpetic neuralgia pain	Lidoderm	Endo Pharmaceuticals (Chadds Ford, PA)
2001	Ethinylestradiol	Contraception	Ortho Evra	Ortho-McNeil Pharmaceutical (Raritan, NJ)
2003	Estradiol	Menopausal symptoms	Climara Pro	Bayer Healthcare Pharmaceuticals

2003	Oxybutynin	Overactive bladder	Oxytrol	Watson Pharma (Corona, CA)
2004	Lidocaine (ultrasound)	Local dermal anesthesia	SonoPrep	Echo Therapeutics (Franklin, MA)
2005	Lidocaine/tetracaine	Local dermal analgesia	Synera	Endo Pharmaceuticals (Chadds Ford, PA)
2006	Fentanyl HCl (iontophoresis)	Acute postoperative pain	Ionsys	Alza, Mountain View, CA
2006	Methylphenidate	Attention deficit hyperactivity disorder	Daytrana	Shire (Wayne, PA)
2006	Selegiline	Major depressive disorder	Emsam	Bristol-Myers Squibb (Princeton, NJ)
2007	Rotigotine	Parkinson's disease	Neupro	Schwarz Pharma (Mequon, WI)
2007	Rivastigmine	Dementia	Exelon	Novartis (East Hannover, NJ)

Table2: Representative transdermal drugs in clinical development:[6]

Drug	Company	Indication	Clinical phase	Delivery technology
AB-1001	Abeille	Nausea and vomiting	Phase 3	Passive
acyclovir	Transport	Herpes labialis	Phase 2	Iontophoresis
buprenorphine	Purdue Pharma	Pain	Phase 3	Passive
fertility hormone	Vyteris / Ferring	Female infertility	Phase 1	Iontophoresis
granisetron	Prostrakan	Nausea and vomiting	Pre-registration	Passive
heat-labile enterotoxin of *E. coli*.	Iomai	Travelers'diarrhea	Phase 2	Skin abrasion
human growth hormone	TransPharma / Teva	Growth hormone deficiency	Phase 1	Thermal ablation
influenza vaccine	Becton Dickinson / Sanofi-Pasteur	Influenza prophylaxis	Pre-registration	Microneedles
insulin	Altea	Diabetes mellitus	Phase 1	Thermal ablation
insulin	Phosphagenics	Diabetes mellitus	Phase 2	Vesicular carrier
ketoprofen	ZARS	Osteoarthritis	Phase 3	Heat enhancement
parathyroid hormone (1–34)	Zosano	Osteoporosis	Phase 2	Microneedles
sufentanil	Durect / Endo	Chronic pain	Phase 2	Passive
testosterone	Acrux / VIVUS	Female sexual dysfunction	Phase 2	Metered dose transdermal spray
testosterone	MacroChem	Male hypogonadism	Phase 2	Chemical enhancer (SEPA)
testosterone	Procter & Gamble / Watson	Hypoactive sexual desire disorder	Pre-registration	Passive
triamcinolone acetonide	Echo Therapeutics	Dermatoses	Pre-registration	Chemical enhancer (AzoneTS)

These patches characteristically composed of four layers: an impermeable backing membrane; a drug reservoir; a semi-permeable membrane that may serve as a rate-limiting barrier; and an adhesive layer. Other designs include the drug into a solid polymer matrix. Matrix systems composed of three layers, by eliminating the semi-permeable membrane or two layers, incorporating the drug directly into the adhesive.

To an extent transdermal patches has replaced by metered liquid spray, gel or other topical formulation which when

applied to the skin , upon evaporation or absorption, leave small lipophilic drugs into the stratum corneum, which in turn serves as the drug reservoir for extended release into the viable epidermis over hours. For example, testosterone gels have been in use for several years and a transdermal spray has been recently approved for estradiol delivery.

Second-generation transdermal delivery systems:

The second generation of transdermal delivery systems recognizes the importance of skin permeability enhancement to explore the scope of transdermal drugs.However, enhancement methods developed in this generation, like conventional chemical enhancers, non-cavitational ultrasound, and iontophoresis and still struggled with the balance between achieving increased delivery across stratum corneum, and protecting deeper tissues from damage.

Conventional chemical enhancers:

To enhance skin permeability, second-generation delivery strategies had turned largely towards chemical enhancers.One challenge of this approach is to increased permeation enhancement of small molecules, yet it increased skin irritation. A numbers of these enhancers which increased skin permeability without irritations had been used successfully to deliver small molecules, but have hadshow limited delivery of hydrophilic compounds or macromolecules.

Iontophoresis:

This approach mainly basedon electrical driving force for transport of drug molecules across stratum corneum.Electrophoresis can moved Charged drug molecule while electro-osmotic flow of water generated by the preferential movement of mobile cations (e.g., Na+) instead of fixed anions (e.g., keratin) in the stratum corneum can move weakly charged and uncharged compounds .The strongest point of iontophoresis is that the rate of drug delivery associated with the electrical current, which can be easily controlled by a microprocessor.

Non-cavitational ultrasound:

Ultrasound was firstly recognized as a skin permeation enhancer when it was discovered that massaging anti-inflammatory agents into the skin using ultrasonic heating probes increased efficacy. Although it was hypothesized that the pressure gradients and oscillation associated with ultrasound act as a driving force to move drug molecules into the skin. It appears that in this approach,the main effect was to disrupt stratum corneum structure and thereby enhance permeability.

Third-generation transdermal delivery systems:

The third generation of transdermal delivery systems was poised to make significant impact on drug delivery because it mainly targets its effects to the stratum corneum. This approach enables almost complete disruption of the stratum corneumwall and thereby more effective transdermal drug delivery, while protecting deeper tissues together.In this way, novel chemical enhancers, ,cavitational ultrasound,electroporation and more recently microneedles, thermal ablation and microdermabrasion (Arora et al) have been shown to deliver macromolecules, includingvaccines and therapeutic proteins, across the stratum corneumin human clinical trials.

Combinations of chemical enhancers:

Suitably designed combinations of chemical enhancers can balancebetween enhancement and irritation.This approach enables a strategy to target effects that not only enhance skin permeability in the stratum corneum, but also avoid irritation in deeper tissues where the formulation composition becomes diluted or otherwise altered.for example, for a combination of sodium laurethsulfate (an anionic surfactant) and phenyl piperazine (a compound with aromatic nitrogen) at concentrations of 0.35 and 0.15 wt%, respectively, in a 1:1 mixture of phosphate-buffered saline and ethanol. In vitro screening results were validated with in vivo delivery of a peptide (leuprolide acetate) to hairless rats.

Biochemical enhancers:

Recently, peptides have been examined as enhancers of skin permeability. Experiment showed that natural pore-forming peptide (magainin), can be used to enhance skin permeability by a mechanism proposed to target bilayer disruption in stratum corneum lipids but not in deeper tissue.

Electroporation:

It is a well-known method. The short, high-voltage pulses used to reversibly disrupt cell membranes for gene transfection and for other applications. Electroporation also used to disrupt lipid bilayer structures in the skin.Recently, electroporation was shown to deliver a model peptide vaccine into the skin of mice to generate a strong cytotoxic T lymphocyte response.

Cavitational ultrasound:

In addition to generate heat, ultrasound is also generate cavitation, which is the oscillation, formation, and, collapse of bubbles in an ultrasonic pressure field. Cavitation is generatedonly under specific conditions (e.g., low-frequency ultrasound)The opportunity for transdermal drug delivery is that cavitation bubbles collect the energy of ultrasound and thereby enable targeted effects at the site of bubble activity. The expected mechanism of cavitational ultrasound is that bubbles oscillate and collapse at the surface of skin, which generates localized shock waves and liquid microjets directed at the stratum corneum. This disrupts stratum corneum lipid structure and thereby increases skin permeability for up to many hours without damaging deeper tissues.

Microneedles:

Microneedles developed as a means to deliver drugs into the skin by invasive manner. Solid microneedles have been shown to painlessly pierce the skin to increase skin permeability to a variety of small molecules, nanoparticlesand proteins from an extended-release patch.Microneedles have been dip coated with a variety of compounds such as small molecules, DNA,proteins, and virus particles.In a recent study, naltrexone was administered to healthy volunteers whose skin was pre-treated with microneedles51. After applying the naltrexone patch, threapeutic levels of naltrexone achieved.

Thermal ablation:

This approach mainly based on heating the skin surface to generate micron-scale perforations in the stratum corneum.Animal studies have revealed the ability of thermal ablation to deliver a number of compounds, such as interferon α-2b and human growth hormone. Skin heating has been achieved using ohmicmicroheaters and radio-frequency ablation.

Microdermabrasion:

A way to remove the stratum corneum barrier employs abrasion bysimply using sandpaperor microdermabrasion. Microdermabrasion is a widely used method to alter and remove skin tissues for cosmetic purposes.

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