TRANSDERMAL PATCH : A RECENT REVIEW TO TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Transdermal drug delivery system was administrated by the transdermal route to give the various advantage of being painless and overcomes the drug delivery difficulties through oral route. The formulation using the skin as a way of drug entry, its adhere the surface of skin , and access underlying systemic circulation and lymphatic networking of drug delivery. More drug delivery through skin for systemic effect, called first used transdermal drug delivery used in 1981 by FDA, (transderm scop) used to prevent nausea and vomiting associated with motion sickness. A transdermal patch properly design and developed for a drug , novel drug delivery system can minimize the complication associated with traditional method of delivery e.g., drugs that endure partial and entire deterioration before reach the site of action could be effectively delivered with improve bioavailability, patient compliance, reduce systemic side effect. This review article can describes the various methods of preparation types of transdermal patches such as reservoir type, matrix type, membrane matrix, micro reservoir and drug in adhesive patches. These transdermal dosage form of various methods can evaluated also been in reviewed.

Keyword :- Transdermal delivery, Transdermal patch, Matrix patch, Reservoir Type, Drug-In-Adhesive patches, Micro Reservoir patches.

1.0 INTRODUCTION

During some few year later, the design and development of novel drug delivery systems assemble the drug molecules has been updated. This novel drug delivery system can also be improve the drug efficacy and improve patient compliance and therapeutic benefits. The design and development of particular drug dosage form can associate with different conventional method of delivery of drug[1]. A transdermal patch of transdermal drug delivery system administered to specific dose of drug through skin membrane and blood stream. The first marketed product of transdermal patch approved in 1981 by FDA. Following transdermal patches are available in market e.g. scopolamine (hyoscine) for motion sickness, clonidine for cardiovascular disease, nicotine for smoking cessation , fentanyl for chronic pain[2]. Transdermal drug delivery system provided controlled release of the drug into the patient blood level profile, develop in reduction in side effects and, sometime, improve efficacy of dosage forms. Transdermal delivered drug can avoid the risk and inconvenience of IV therapy, it also provide less chance of an overdose and under dose, easily allow to termination[3]. During 30 year past, advance approaches in drug formulation and systematic route of administration have made. The drug transport through the skin (tissue) has high. The main aim of transdermal route of drug delivery into via the systemic circulation through skin at rate with intrapatient variation and minimal inter because transdermal patches are user very convenient, painless, friendly and multi day dosing. The transdermal drug delivery system growth rate is approx to increase 20 % at annually 2015[4].

1.1 Drug across human skin

The skin covers an area of approx 2 sq.m and reaches about blood circulation through the body, offers the barrier against permeability of transdermal absorption of following agents. The drug molecules can penetrate by three pathways or directly across by stratum corneum[14].

1. Sweat ducts
2. Hair follicles
3. Sebaceous gland

The stratum corneum is the outer most layer of skin. It consists of 10 to 15 layer of corneocytes and thickness approx 15 um in dry state 40- 45 um in hydrated. The initial layers of stratum corneum rearrange to form intercellular lipid lamellae. The lipid composition of stratum corneum is behavior like a different form of biological membranes. The keratinocyte molecules must partition into and diffused through the estimated 4-25 lipid lamellae between each keratinocyte. The transdermal route of penetration only based on passive diffusion. Drug must penetrate the stratum corneum because the skin is permeation barrier. When the drug molecules can penetrate the skin membrane across the hair follicles, sweat gland and sebaceous gland through the stratum corneum becomes the primary pathway of skin permeation[15].

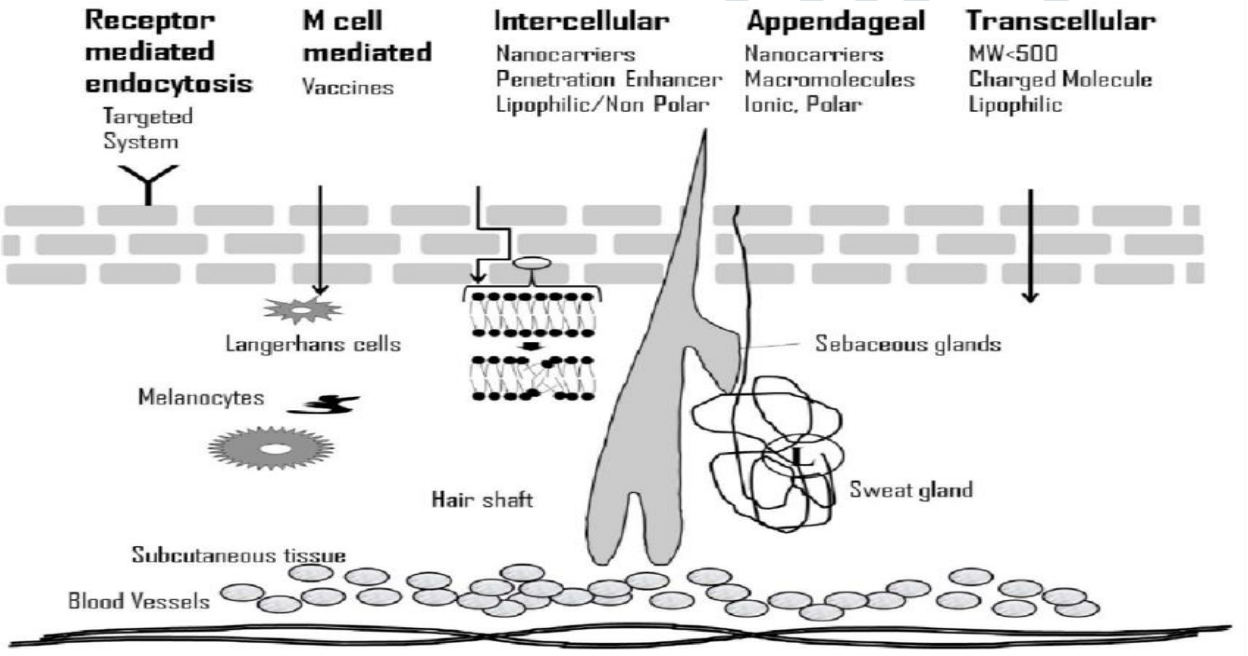

Fig. 1: Transverse section of skin showing routes of penetration[4]

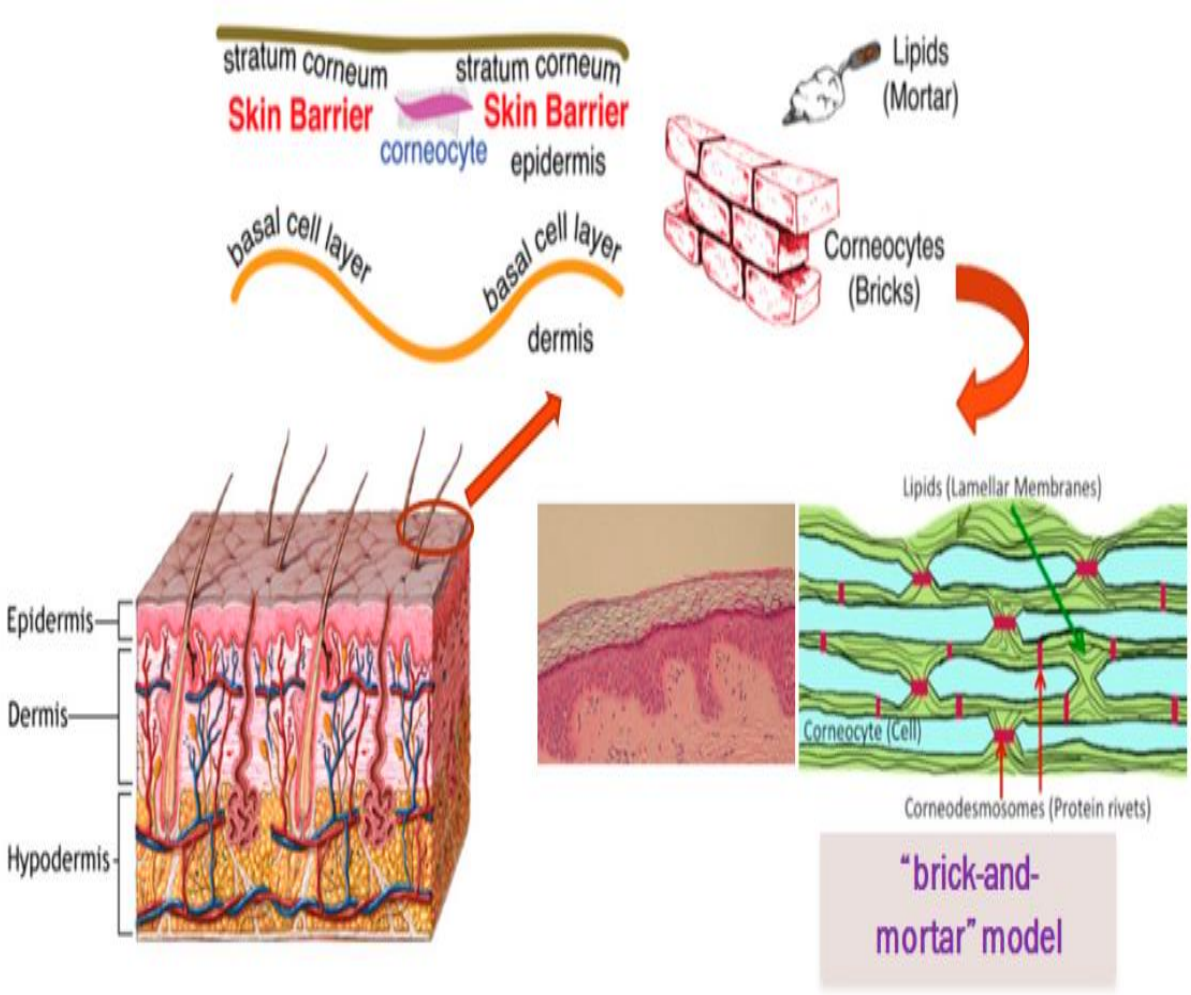

Fig. 2: Structure of stratum corneum according to brick and mortar model[6]

The therapeutic release of drug formulation applied to skin membrane and transport to systemic circulation in multiple stages is involved.

- Diffusion through the SC, via lipidic intercellular pathway
- With the Dissolution and release from the formulation.
- SC into the aqueous viable epidermis and into upper dermis, uptake into the papillary dermis and into microcirculation[5].

1.2 Method for enhancement of transdermal drug delivery[7]

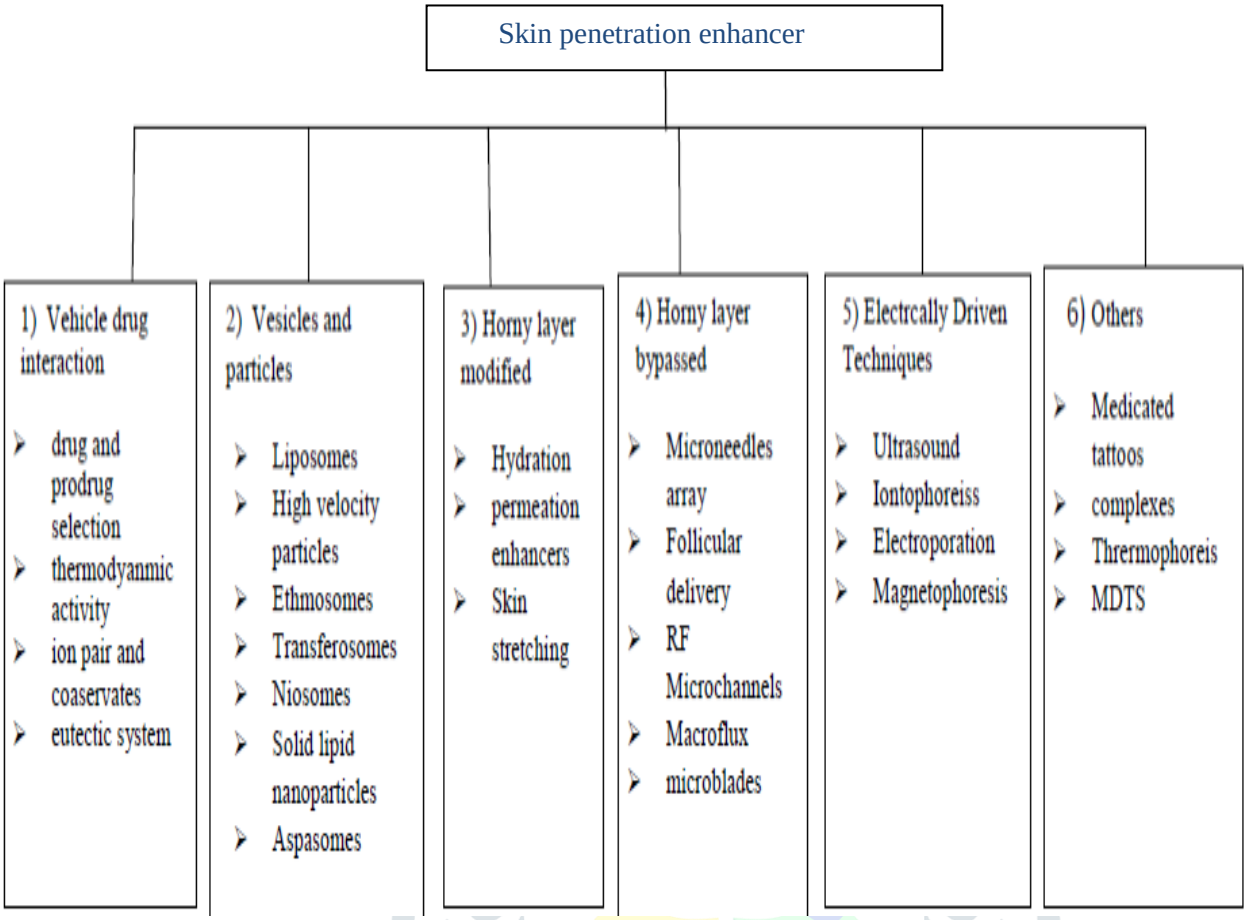

Fig. 3: various methods used to enhance the skin penetration

1.3 Factor affecting transdermal permeation

Table 1: factors affecting transdermal permeation[11,16]

Factors	Explanations
Physicochemical properties of the penetrate molecules	
Partition coefficient	It may altered the chemical modification without affecting the pharmacological activities of drug.
P^H Conditions	P^H value are high or very low can be destructive to the skin
Penetration concentration	Increased concentration of dissolved drug causes a proportional increase in flux. Maintain constant drug constitution for a prolonged period of time
Physicochemical properties of the drug delivery system	
Release characteristics	Solubility of drug in the additives determines the rate release. Interfacial partition coefficient of drug from delivery system to skin tissue. P^H of vehicle
Composition of the drug delivery system	Many drug is not penetrate skin at high rate for therapeutic efficacy the penetration can improve by addition of permeation promoter into drug delivery system.

Table 2: Ideal properties of transdermal drug delivery system[10]

S.No.	Properties	Range
1.	Shelf life	should be up to 2.5 year
2.	Dose frequency	once a daily- once a week
3.	Appearance	should be clear or white color
4.	Packaging properties	should be easily removal of release liner
5.	Skin reaction	should be non irritating
6.	Patch size	should be less than 40 cm^2

Table 3: Ideal properties of drug for TDDS[12]

S.No.	parameter	properties
1.	Dose	should be low
2.	Molecular weight	less than 500
3.	Partition coefficient	log P (-1 AND 3)
4.	Half life in hr	should be 10 or less
5.	Skin reaction	should be non irritating
6.	Skin permeability	should be less than 0.5 x 10^{-3}cm/hr
7.	Oral bioavailability	should be low
8.	Therapeutic index	should be low
9.	Concentration	minute
10.	Dose deliverable	greater than 10mg/day

1.4 Advantages of transdermal drug delivery systems[8]

Transdermal drug delivery system is via transdermal route because this route is use to patient compliance and safe. Transdermal route of drug delivery across skin and shows systemic effects in the body.

- Avoid first pass metabolism
- More patient compliance
- Avoid drug level fluctuation
- Improve pharmacological and physiological response
- Provide use of drug with short biological half life
- Maintain plasma concentration of therapeutic dose
- Avoid incompatibility in gastro intestine
- Extend and sustain duration of activity of drug
- Minimize unwanted side effect
- Provide narrow therapeutic index
- Easy self administered
- Deliver of drug to more specific site
- Most advantage in patient who are unconscious and nauseated

1.5 disadvantage of transdermal drug delivery system[9]

- Local irritation possible at site of action
- Some time itching and edema can cause by drug
- Some time may cause allergic reaction
- Some time not require high blood levels to drug administration
- Molecular weight less than 500 Da
- Drug not suitable , not posses o/w partition coefficient
- The barrier function of skin of change to one site to another site and person to person

2. Transdermal patches[21]

Transdermal patches are used in various field cosmetic, topical and transdermal drug delivery systems. Transdermal patches one type of essential formulation of transdermal drug delivery systems. It is the medicated preparation of topical adhesive patch that is applied on body surface to administered the specific dose of drug via skin and into bloodstream. The patch formulations represent in outcomes growth in many technology, developments, trials and clinical observations. Transdermal patches products were first approved in 1981 by FDA.

2.1 Main basic component of transdermal patch

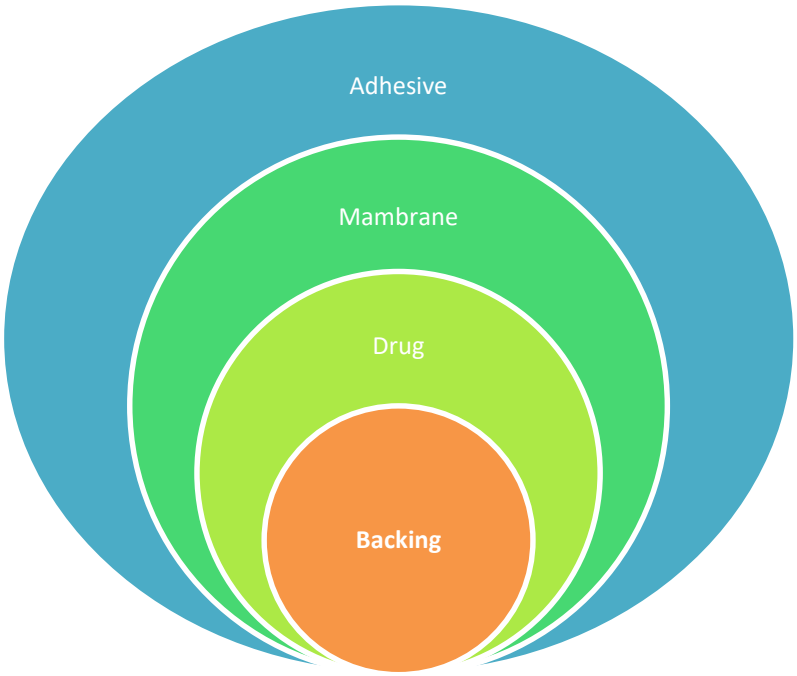

Fig. 3. Basic component of transdermal patch[22]

1. Polymer matrix
2. Drug
3. Permeation enhancer
4. Adhesive
5. Backing laminates
6. Release liner

- **Polymer matrix -** Polymer is very essential component of transdermal drug delivery system. The polymer matrix are control the rate release of drug. It also provided the patch during storage. Those type of many polymer should be use to formulation of patch that is non toxic in nature, polymer should not ne reactive in nature, polymer should be stable, polymer should not be decompose during storage condition, cost of polymer should not be high.

  e.g. - PEG 400 (added to increase the solubility of drug)
  Ethanol (used as co solvent)
  Cellulose derivative
  Zein
  Gelatin
  Shellac
  Waxes
  Polybutadiene, polyvinylchloride, polyvinylprrolidone
  Polyvinyl alcohol etc.

- **Drug substances –** Drug in the transdermal patch which appropriate show action and chemistry. Drug in transdermal patches undergoes extensive first pass metabolism and drug show therapeutic effect in body.
  e.g. – Fenatyl
  Nitroglycerine
  Topiramate
  Atenolol etc.

- **Permeation enhancers –** It provide the high permeability of stratum corneum so that provide more therapeutic effect of drug. That provide skin barrier to promote either interact with preparation that applied on skin itself. Penetration enhancer is not cause loss of electrolyte and body fluid. That should be inert in nature, non toxic, non allergic, predictable duration.
  e.g. – DMSO
  Methanol
  Ethanol etc.

- **Adhesive layer -** It provide the adhesive support to the patch into the skin surface. It also increases the permeability of stratum corneum and gives higher therapeutic effect of drug into body. It not causes irritation, sensitization and should be easily removed, good skin contact, good bonding between laminating layer.

- **Backing laminates –** It is used to provide support. It is able to prevent drug from leaving the dosage form through top of patch. They should be low modulus or high flexibility. They should have optimal elasticity, tensile strength. They also should be chemical compatible with the drug, enhancer, adhesive and other excipients. It also use to protects patch from the outer environment.

  - ✓ High flexibility
  - ✓ Avoid loss of drug
  - ✓ Accept penetrating
  - ✓ Good oxygen transmission
  - ✓ High moisture vapor transmission rate

  e.g. - Vinyl
  Polyethylene
  Polyester
  Polyvinyl chloride
  Heat seal layer

- **Release liner –** it is used to protect the patch during storage. It prevents the loss of drug that has migrated into the adhesive layer during storage. It is provide help to prevent contamination..It is make a base layer, which may occlusive (polyethylene, polyvinylchloride) and nonocclusive (paper fabric) and release coating layer made up of Teflon and silicon.
  e.g. – polyester
  Foil
  Mylar
  Metalized laminates

3.0 - Patch development and various technologies[23]

The development of patch and various technologies are used in the formulation of patches. There are many various major two type of transdermal delivery system of products:

1 – Flexible colored or transparent liquid or semisolid filled reservoir patches

2 – Thin flexible colored or nearly invisible matrix patches

4.0 - Types of transdermal patches[24]

A. Single-layer Drug-in-adhesive

The layer of drug in adhesive in single layer that characterized by the administration of drug delivered into skin in directly contacting adhesive. In case of transdermal drug delivery system , the adhesive not only serves to affix to skin, but also release of drug. That layer of drug formulation containing drug and excipients under a single backing film and temporary linear.

e.g. - deponit

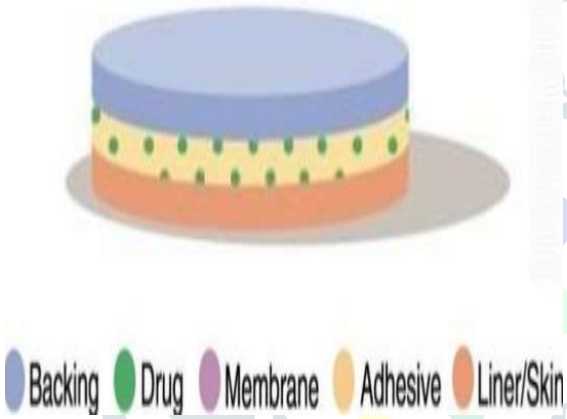

Fig.4 – Single layer of transdermal patches[23]

B. Multi layer drug in adhesive

The layer of multi layer of drug in adhesive that is similar to the single layer of adhesive and also responsible for drug release. One of the layers is rapidly release of drug and other layer can control the release of drug to the reservoir. However the multi layer of addition to membrane between two drugs in adhesive layers or addition of multiple drugs in adhesive layers under a single backing film. This patch also temporary liner-layer and a permanent backing.

Fig.5- Multi layer of transdermal patch

C. Reservoir

The design of reservoir transdermal system that is characterized by the inclusion of liquid compartment of drug containing solution or suspension separated by the adhesive layer and permeable membrane. This patch of also backed by the backing layer. In this type of system the rate of release is zero order.

e.g. – transderm-nitro

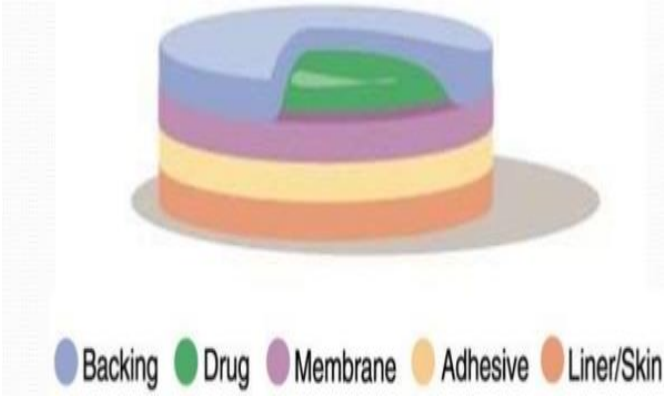

Fig. 6 – Reservoir type transdermal patches[25]

D. Matrix

The matrix system of drug design , layer of semisolid matrix contain a drug in solution and suspension which is directly contact with release liner. The component responsible for the skin adhesion is incorporated in layout and forms concentric configuration around the semisolid matrix. It is also known as monolithic device.

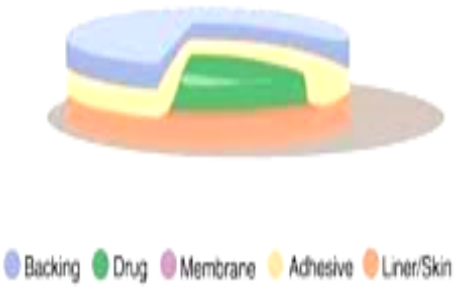

Fig. 7- Matrix type transdermal patches[28]

5.0 : Evaluation parameter of patches[30,33]

1. Thickness of patches
2. Weight variation
3. Drug content
4. Folding endurance
5. Content uniformity
6. Tensile strength
7. Moisture content
8. Microscopic study (SEM)
9. Water vapor transmission studies
10. Flatness
11. In-vitro drug release studies
12. In- vitro skin permeation studies

1. Thickness of patches

Thickness of patches of drug is measured by using a digital micrometer and the average thickness and standard deviation is determined to ensure the thickness of prepare patch at different point. The thickness of film is determined by traveling microscope dial gauge, screw gauge.

2. Weight variation

A specific 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. The prepared patches are dried at 60^0 c for 4hrs before testing.

3. Drug content

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

4. Folding endurance

Folding endurance evaluation involves determining the folding capacity of the patches. Folding endurance determined by repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

5. Content uniformity

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

6. Tensile strength

Tensile strength = F/a.b(l+L/l)

F is the those required to break; a is width of film; b is thickness of film; L is length of film; l is elongation of film at break point.

7. Moisture content

The prepared films are to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. after 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

% Moisture content = Initial weight – Final weight x 100 / Final weight

8. Microscopic study (SEM)

Scanning electron microscopy is attest process that scan a sample with an electron beam to produce a magnified image for analysis. The method is also as SEM analysis or microscopy and is used very effectively in micro analysis and failure analysis of solid inorganic material.

9. Water vapor transmission studies (WVT)

For the determination of WVT, weigh one gram of calcium chloride and place it in previously dried empty vials having equal diameter. The polymer films are pasted over the brim with the help of adhesive like silicon adhesive like silicon adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials are accurately weighed and placed in humidity chamber maintained at 68%RH. The vials are again weighed at the end of every 1st day , 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch. In other reported method, desiccators were used to place vials, in which 200 ml of saturated sodium bromide and saturated potassium chloride solution were placed. The desiccators were tightly closed and humidity inside the desiccators was measured by using hygrometer. The weighed vials were then placed in desiccators and procedure was repeated.

WVT = W/ST

W is the increase in weight in 24 hrs; S is area of film exposed (cm^2); T is exposure time.

10. **Flatness**

One strip is cut from the center and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

% constriction = $[(I_1-I_2)/I_1]$ x100

I_1 = initial length of each strip

I_2 = final length of each strip

11. In vitro drug release studies[34]

The paddle over disk method (USP apparatus V) is employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness are 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 ($_p$H 7.4), and the apparatus is equilibrated to 32 ± 0.5^{0}C. the paddle is then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Sample (5ml aliquots) can be withdrawn at appropriate time intervals up to 24 hrs and analyzed by UV spectrophotometer or HPLC. The experiment is to performed in triplicate and the mean value can be calculated.

12. **In vitro skin permeation studies**[35]

An in vitro permeation studies can be carried out by using diffusion cell. Full thickness abdominal skin of male Westar rats weighing 200 to 250 gm. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of skin is thoroughly cleaned with distilled water to remove any adhering tissue or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer $_p$H 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 ± 0.5^0 C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the

receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Sample are to be filtered through filtering medium and can be analyzed spectrophotometrically or HPLC. Flux can be determined directly as the slop of the curve between the steady-state values of the amount of drug permeated (mg cm-2) vs. time in hrs and permeability coefficient were deduced by dividing the flux by the initial drug load (mg cm-2).

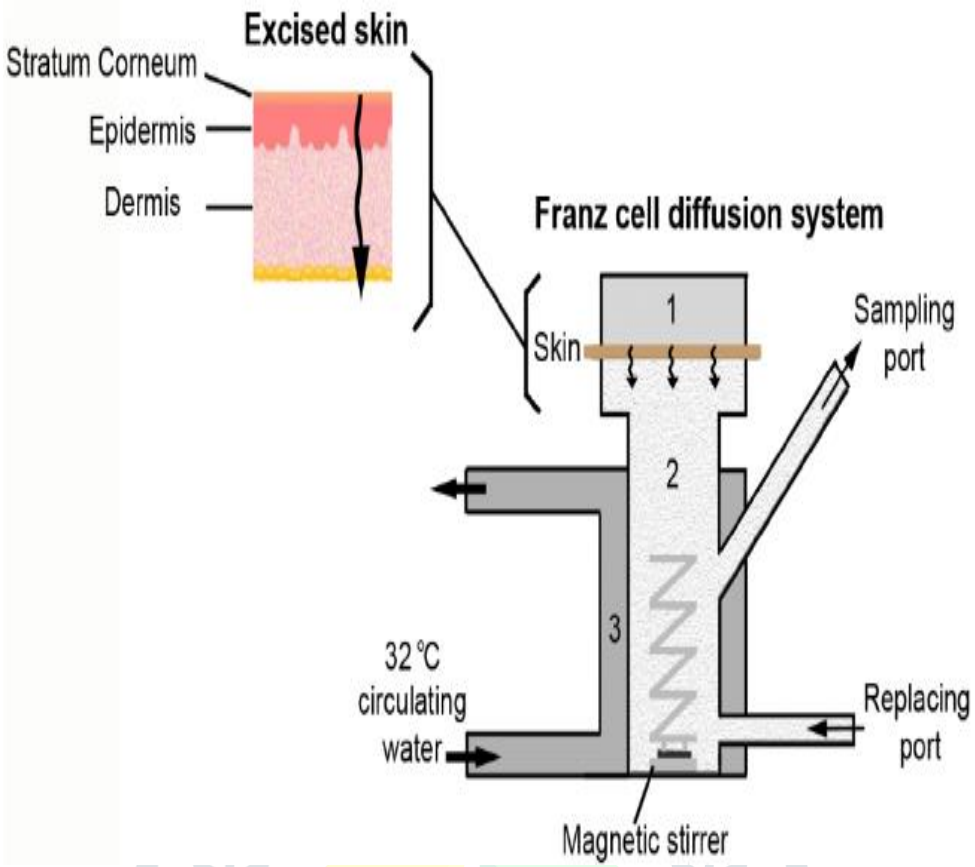

Fig. 8. Diffusion cell for in vitro experiments[38]

Table 4 : Marketed product of transdermal drug delivery system[40]

S.No	Product	Active drug	Type of transdermal patch	purpose
1.	Transderm-scop	Scopolamine		Motion sickness
2.	Deponit	Nitroglycerine	Drug in adhesive	Angina pectoris
3.	Estraderm	Estradiol	Membrane	Postmenstrual syndrome
4.	Duragesic	Fentanyl	Reservoir	Pain relief
5.	Androderm	Testoseterone	Membrane	Hypogonadism syndromes
6.	Captopatch TTS	Clonidine	Membrane	Hypertension
7.	Combipatch	Estrsdiol	Matrix	Postmenstrual syndroms
8.	Esclim	Estradiol	Matrix	Harmone replacement therapy
9.	Fempatch	Estradiol	Matrix	Postmenstrual syndromes
10.	Lidoderm	Lidocane	Drug in adhesive	Angina pectoris
11.	Ortho Evra	Estradiol	Drug in adhesive	Postmenstrual syndromes
12.	Testrodream TTS	Testesterone	reservoir	Hypogonadism in male
13.	Habitraol	Nicotine	Drug in adhesive	Smoking cessation
14.	Climaderm	Estradiol	Matrix	Postmenstrual syndromes
15.	Fematrix	Estrogen	Matrix	Postmenstrual syndromes
16.	Nuvelle TS	Estradiol	Drug in adhesive	Harmone replacement therapy
17.	Oxytrol	Oxybutynin	Matrix	Overactive bladder
18.	Transderm-nitro	Nitroglycerin	Reservoir	Angina pectorise
19.	Nitrodur	Nitroglycrine	Matrix	Angina pectoris
20.	Nupetch 100	Diclofenac diethyl amine	Drug in adhesive	Anti-immflamatry

Conclusion

In case of transdermal patch the drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. Transdermal drug delivery systems (TDDS) are dosage forms involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. The adhesive (transdermal patch) of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. This review article provides valuable important information regarding the formulation and development, evaluation aspects of transdermal drug delivery systems. TDDS is a realistic practical application as the next generation of drug delivery system.

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