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A Review on Transdermal Drug Delivery Patches

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ABSTRACT

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Transdermal drugs are a self- contained dosage form. Transdermal drug delivery systems used to overcome the difficulties of drug delivery through the oral route. Often, this promotes the healing of an injured area of the body. An advantage of a transdermal drug delivery route over other types of drug delivery such as oral, topical, intravenous, intramuscular, etc. is that the transdermal patch provides a controlled release of the medication. Also, Transdermal drug delivery systems improve the therapeutic efficacy and safety of drugs by specific sites within the body, thereby reducing both the size and number of doses. This review article covers advantages, the structure of the skin, routes of drug penetration, various basic components of a transdermal patch, and methods for the preparation of transdermal patches, evaluation parameters of transdermal patches.

INTRODUCTION:

Transdermal drug administration is the topical application of agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. Transdermal products are designed to maximize the flux through the skin into the systemic circulation and reduce the retention and metabolism of the drug in the skin. [(1)]There designing is done in such a manner that therapeutically effective amount of drug is delivered across the patient's skin. Transdermal drug delivery has been the leading edge over injectables and oral routes by enhancing patient compliance and bypassing the first-pass metabolism respectively. [(2)]

Advantages of Transdermal drug delivery:

1. It Protects drugs from Hepatic first-pass metabolism, salivary metabolism, and intestinal metabolism.

2. Self-medication is possible.

3. In case of any emergency, removing the patch at any time during therapy can instantly stop drug input.

4. Drugs showing GI irritation and absorption can be administered in this form.

5. The continuous, non-invasive infusion can be achieved for drugs with short biological half-lives, which would otherwise require frequent dosing.

6. Due to the reduced frequency of dosing, there is better patient compliance.

7. Therapeutic failures associated with irregularities in the dosing with conventional therapies can be avoided.

8. The adverse effects are reduced due to a steady and optimum blood concentration-time profile.

9. The risks, pain, and inconvenience associated with parenteral therapy are avoided.

10. The release is more prolonged than oral sustained drug delivery systems.

11. The daily dose of the drug required is lower than that with conventional therapies.

12. The drug release is such that there is a predictable and extended duration of the activity. (1, 3)

Disadvantages of Transdermal drug delivery:

1. Possibility of skin irritation due to one or many of the formulation components.

2. Binding of the drug to the skin may result in dose dumping.

3. It can be used only in chronic conditions where drug therapy is desired for a long period of time including hypertension, angina, and diabetes.

4. Lag time is variable and can vary from several hours to days for different drug candidates.

5. Cutaneous metabolism will affect the therapeutic performance of the system.

6. Transdermal therapy is suitable for potent drugs only.

7. Transdermal therapy is not suitable for ionic drugs.

8. It cannot deliver drugs in a pulsatile fashion. (1, 3)

Structure of Skin (fig.1):(3,4)

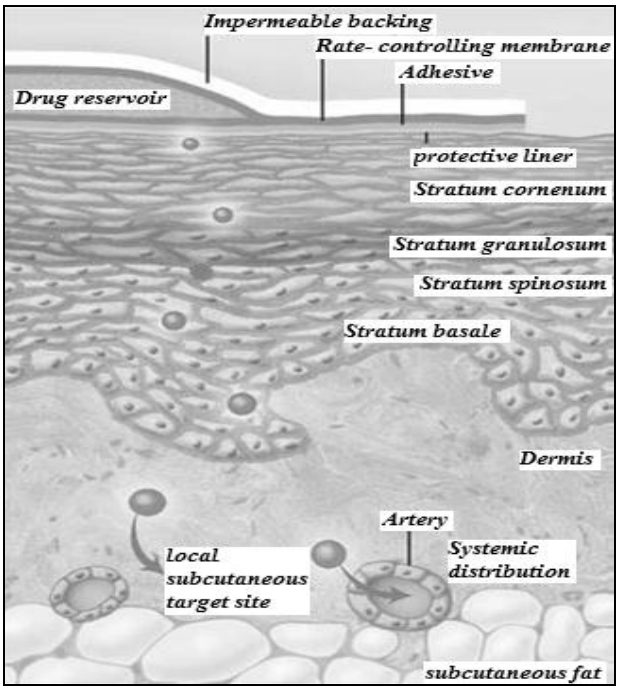

Figure No. 1: Transdermal drug delivery and skin structure

Skin is the largest organ of the integumentary system of the human body.

The functions of the skin:

1. It keeps the body and organs intact.

2. It protects the internal organs from pathogens, chemicals, and other external threats.

3. It acts as a water-resistant barrier and reduces trans-epidermal water loss(TEWL).

4. It regulates the temperature of the body.

5. It acts as a storage center for water and lipids and helps in synthesizing vitamin D.

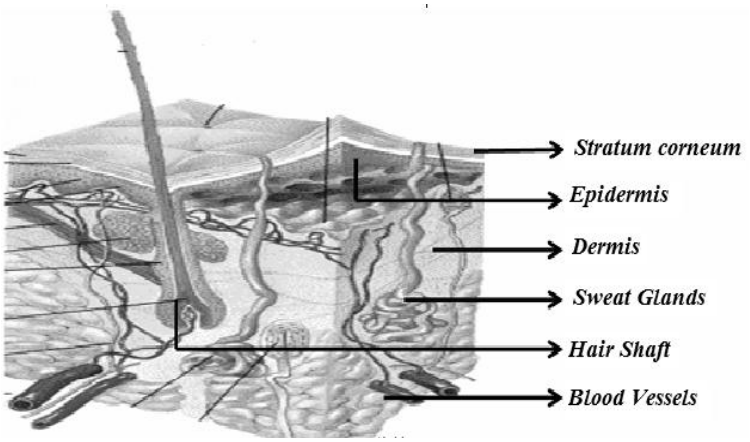

Figure No. 2: Structure of human skin

Three main layers of Skin:

1) Epidermis: It protects the body organs from infection and prevents the evaporation of water. The epidermis is the outermost layer of the skin, which consists of stratified squamous epithelium with an underlying basal lamina. It can be further subdivided into five distinct layers, which provide barrier resistance to the skin. The five layers of the epidermis are arranged in the order from top to bottom are stratum corneum, stratum lucidum (In palms of hands and bottoms of feet), stratum granulosum, stratum spinosum, and stratum basale.

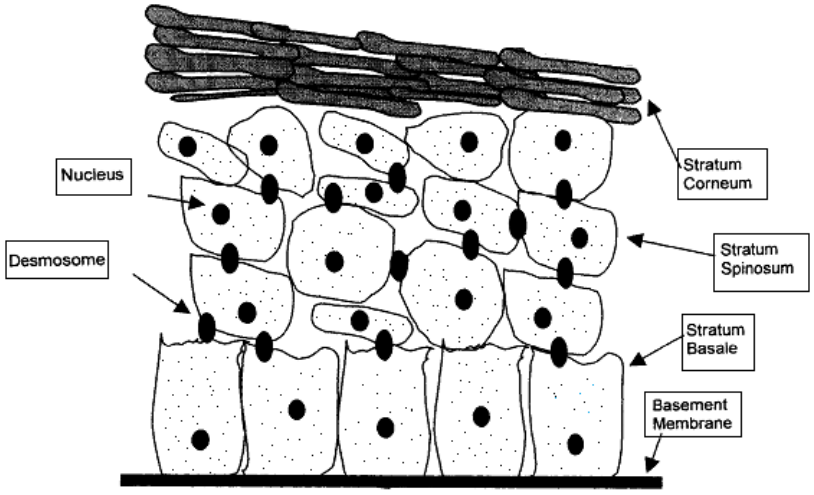

Figure No. 3: Various layers of the Epidermis

2) Dermis: It comprises of connective tissue and cushions the body from stress and strain. It is a 2-3 mm thick layer present beneath the epidermis and provides a flexible support structure to the skin. It has hair follicles, sweat glands, sebaceous glands, apocrine glands, lymphatic vessels including blood vessels. This layer provides the synthesis of collagen and elastin. The dermis is tightly linked to the epidermis by a basement membrane and helps in the regulation of temperature, pain, and pressure in the body. The sense of touch and heat to the skin are provided by the nerve endings that are present in this layer.

3) Hypodermis: It consists of subcutaneous adipose tissues and mainly acts as a thermal barrier. It is the deepest layer of the skin, also known as subcutaneous tissue. It includes adipose tissue (fat cells), connective tissues, macrophages, and fibroblasts. [3, 4]

Routes of penetration:

The diffusant has two potential entry routes to the blood vasculature; through the epidermis itself or diffusion through the shunt pathway, mainly hair follicles with their associated sebaceous glands and the sweat ducts. Therefore, there are two major routes of penetration.

1. Transcorneal penetration

a. Intracellular penetration:

Drug molecule passes through the cells of the stratum corneum. It is mainly seen in the case of hydrophilic drugs. As stratum corneum hydrates, water accumulates near the outer surface of the protein filaments. Polar molecules appear to pass through this immobilized water.

b. Intercellular penetration:

Non-polar substances follow the route of intercellular penetration. These molecules dissolve in and diffuse through the non- aqueous lipid matrix imbibed between the protein filaments.

2. Transappendegeal penetration

This is also called as the shunt pathway. In this route, the drug molecule may transverse through the hair follicles, the sebaceous pathway of the pilosebaceous apparatus, or the aqueous pathway of the salty sweat glands. The trans appendageal pathway is considered to be of minor importance because of its relatively smaller area (less than 0.1% of total surface). However, this route may be of some importance for large polar compounds.

The route through which permeation occurs is largely dependent on Physico-chemical characteristics of penetrant, most importantly being the relative ability to partition into each skin phase. The transdermal permeation can be visualized as a composite of a series in sequence as:

1. Adsorption of a penetrant molecule onto the surface layers of stratum corneum.

2. Diffusion through stratum corneum and viable epidermis.

3. Finally through the papillary dermis into the microcirculation.

The viable tissue layer and the capillaries are relatively permeable and the peripheral circulation is sufficiently rapid. Hence diffusion through the stratum corneum is the rate-limiting step. The stratum corneum acts as a passive diffusion medium. [5]

Basic components of transdermal patches:

1. Polymer Matrix

The Polymer controls the release of the drug from the device.

a. Natural Polymers: Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch, etc.

b. Synthetic Elastomers: Polybutadieine, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene, etc.

c. Synthetic Polymers: Polyvinyl alcohol, Polyvinylchloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate, Epoxy, etc.

2. Drug

For successfully developing a transdermal drug delivery system, the drug should be chosen with great care.

Selection of drug for TDDS Patch

1. Dose should be low i.e. <20mg/day
2. Half-life should be 10hrs or less.
3. Mol. Wt should be <400.
4. The partition coefficient should be log P (octanol-water) between1-4.
5. Skin permeability coefficient should be < 0.5 X 10-3cm/h.
6. Drugs should be non-irritating & non-sensitizing to skin.
7. Oral bioavailability should below.

3. Permeation Enhancers

These are compounds that promote skin permeability by altering the skin as a barrier to the flux of the desired penetrant. These may conveniently be classified under the following main headings:

a. Solvents

These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids.

Examples

Water alcohols – methanol and ethanol;

Alkyl methyl sulfoxides: dimethyl sulfoxide,

Alkyl homologs: methyl sulfoxide dimethyl acetamide pyrrolidones: 2 pyrrolidones,

b. Surfactants

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

i. Anionic Surfactants: e.g. Dioctyl sulphosuccinate, Sodium lauryl sulfate

ii. Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc.

iii. Bile Salts: e.g. Sodium ms taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

c. Miscellaneous chemicals

These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents. Some potential permeation enhancers have recently been described but the available data on their effectiveness sparse. These include eucalyptol, di-o-methyl-ß-cyclodextrin, and soybean casein.

4. Other excipients

a. Adhesives:

The fastening of all transdermal devices to the skin has so far been done by using a pressure-sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally.

Both adhesive systems should fulfill the following criteria:

i. should adhere to the skin aggressively, should be easily removed.

ii. Should not leave an unwashable residue on the skin.

iii. Should not irritate or sensitize the skin.

The face adhesive system should also fulfill the following criteria:

i. Physical and chemical compatibility with the drug, Excipients, and enhancers of the device of which it is a part.

ii. Permeation of drugs should not be affected.

iii. The delivery of simple or blended permeation enhancers should not be affected.

b. Backing membrane:

Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent the drug from leaving the dosage form through the top, and accept printing. It is an impermeable substance that protects the product during use on the skin e.g.metallic plastic laminate, plastic backing with an absorbent pad and occlusive base plate (aluminum foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminum foil disc), etc.[6,7,8,9]

Types of Transdermal Patches:

A. Single-layer Drug-in-Adhesive: In this system, the drug is present in the adhesive layer. In this type of patch, the adhesive layer not only serves to adhere to the various layers

together, along with the entire system to the skin but is also responsible for the release of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

B. Multi-layer Drug-in-Adhesive: The multi-layer drug-in-adhesive patch is similar to the single-payer system in that both adhesive layers are also responsible for the release of the drug. One of the layers is for the immediate release of the drug and the other layer is for control release of drug from the reservoir. This type of system is different because one layer is separated from another layer of drug-in-adhesive by a membrane (but not in all cases). This patch has a temporary liner-layer and permanent backing. (Fig 4)

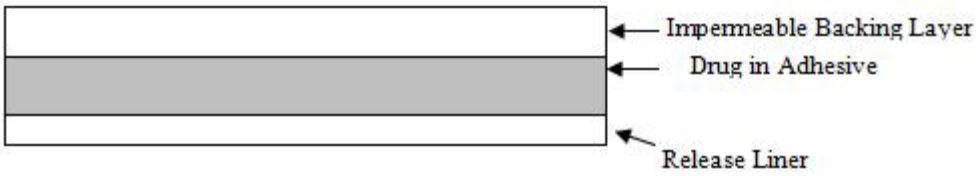

Figure No. 4: Design of drug in adhesive type transdermal patch

C. Reservoir: The reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also having the backing layer. In this type of system, the rate of release is zero order. (Fig 5)

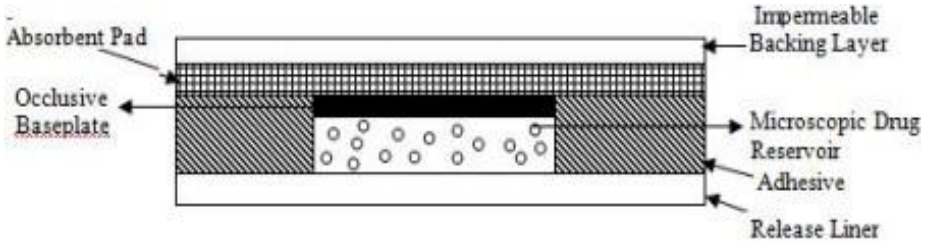

Figure No. 5: Design of reservoir type transdermal patch

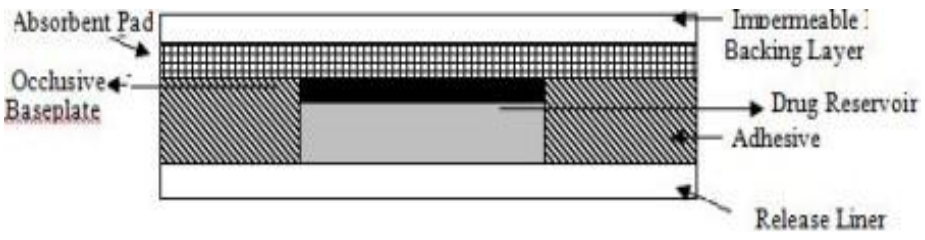

Figure No. 6: Design of matrix type transdermal patch

D. Matrix: The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer. Also known as a monolithic device. (Fig 5) [10,11,12]

Various methods for the preparation of TDDS:

1. Circular Teflon mould method

Polymers in various ratios are dissolved in an organic solvent. The calculated amount of drug is dissolved in half the quantity of the same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Plasticizer (e.g., Di-N-butyl phthalate) is added into the drug-polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular Teflon mold. The molds are to be placed on a leveled surface and covered with an inverted funnel to control solvent vaporization in a laminar flow hood model with an airspeed of 0.5 m/s. The solvent is allowed to evaporate for 24 h. The dried films are to be stored for another 24 h at 25±0.5°C in a desiccator containing silica gel before evaluation to eliminate aging effects. Obtained films are to be evaluated within one week of their preparation.

2. Asymmetric TPX membrane method

A prototype patch can be fabricated for this a heat-sealable polyester film with a concave of 1cm diameter will be used as the backing membrane. The drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1- pentene)} asymmetric membrane, and sealed by an adhesive. These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°C to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in a coagulation bath (maintained the temperature at 25°C). After 10 minutes of immersion, the membrane can be removed, air-dried in a circulation oven at 50°C for 12hr.

3. Mercury substrate method

The drug is dissolved in polymer solution along with plasticizer. It is followed by stirring for 10-15 minutes to produce a homogenous dispersion and poured into a leveled mercury

surface, covered with an inverted funnel to control solvent evaporation.

4. "IPM membranes" method

The drug is dispersed in a mixture of water and propylene glycol containing carbomer-940 polymers and stirred for 12 h in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of tri-ethanolamine. Buffer (pH 7.4) can be used to obtain solution gel if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM (isopropyl myristate) membrane.

5. "EVAC membranes" method

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. The 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 the backing layer. A rate-controlling membrane will be placed over the gel and the edges are sealed by heat to obtain a leak-proof device.

6. Aluminum backed adhesive film method

The transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminum backed adhesive film method is a suitable one. For the preparation of the same, chloroform is used as a solvent. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custom-made aluminum former is lined with aluminum foil and the ends blanked off with tightly fitting cork blocks.

7. Proliposome / Proniosome based TDDS

The proliposomes are prepared by the carrier method using the film deposition technique. From the earlier reference, the drug and lecithin ratio (e.g., 0.1: 2.0) may be used as an optimized one. The proliposomes are prepared by taking mannitol powder (e.g., 5 mg) in a round bottom flask which is kept on a heating water bath and the flask is rotated. It is followed by vacuum drying. Drug and lecithin are dissolved in a suitable organic solvent mixture. An aliquot (e.g.0.5 ml) of organic solvent is introduced into the round-bottomed

flask. After complete drying, the second aliquot (e.g., 0.5 ml) of the solution is to be added. After the last loading, the flask containing proliposomes is connected with a lyophilizer and subsequently, drug-loaded mannitol powders (proliposomes) are placed in a desiccator overnight and then sieved through the suitable mesh. The collected powder is transferred into a glass bottle and stored at the freezing temperature until characterization.

8. Free film method

The free film of cellulose acetate is prepared by casting on the mercury surface. A polymer solution is prepared using a suitable organic solvent. The required amount of plasticizer is incorporated into the polymer solution. A small volume of the polymer solution is poured in a glass ring that is placed over the mercury surface in a glass Petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the Petri dish. The film formation is noted by observing the mercury surface after the complete evaporation of the solvent. The dried film is separated and stored between the sheets of wax paper in a desiccator until use.

9. Glass Substrate Method

The polymeric solutions have kept aside for swelling then the required quantity of plasticizer and drug solution is added and stirred for 10 min. Further, it keeps aside for some time to exclude any entrapped air and is then poured in a clean and dry an umbra Petri plate. The rate of solvent evaporation is controlled by inverting a glass funnel over the Petri plate. After overnight, the dried films are taken out and stored in desiccators.[13,14, 15]

Evaluation parameters:

The evaluation of patches was carried out as per the following parameters.

1. The thickness of the patch: The thickness of the drug-loaded patch is measured by using a digital micrometer and the average thickness of the transdermal film is determined by traveling microscope dial gauge, screw gauge, or micrometer at different points of the film.

2 Weight uniformity: The prepared patches are dried at 60ºC for 4 hrs. before testing. A specified area of patch is to be cut in different parts of the patch and weigh in the digital balance. The average weight and standard deviation values are to weight.

3. **Folding endurance:** A strip of a specific area is to be cut evenly and repeatedly folded at the same place until it breaks. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

4. **Percentage moisture content:** The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage of moisture content from the below-mentioned formula.

$$\% \text{ Moisture content} = \frac{\text{Initial weight - Final weight} \times 100}{\text{Final weight}}$$

5. **Content uniformity test:** 10 patches are selected and content is determined for individual patches. If out of 10 patches have content between 85% 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 ranged from 85% to 115%, then the transdermal patches pass the test.

6. **Moisture uptake:** Weighed films are kept in desiccators at room temperature for 24 hrs. These are then taken out and exposed to 84% relative humidity using a saturated solution of potassium chloride in desiccators until a constant weight is achieved. % moisture uptake is calculated as given below.

$$\% \text{ Moisture uptake} = \frac{\text{Final weight-Initial weight} \times 100}{\text{Initial weight}}$$

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

8. **Shear adhesion test:** 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, degree of cross-linking, and the composition of the polymer, type, and the amount of tackle added.

9. **Peel adhesion test:** In this test, the force required to remove an adhesive coating from a test substrate is referred to as peel adhesion. The molecular weight of the adhesive polymer, the type and amount of additives are the variables that determine peel adhesion properties. A single tape is applied to a stainless steel plate or backing membrane of choice and then the tape is pulled from the substrate at a 180ºC angle, and the force required for tape removed is measured.

10. **Water vapor transmission studies:** For the determination of water vapor transmission, weigh one gram of calcium chloride and place it in previously dried empty vials having an equal diameter. The polymer films are posted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then the vials are accurately weighed and placed in the 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 methods, 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 a hygrometer. The weighed vials were then placed in desiccators and procedure was repeated. VT=W/ST W is the increase in weight in 24 hrs is an area of film exposed (cm^2); T is exposure time.

11. **Rolling ball tack test:** This test measures the softness of a polymer that relates to talking. 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 the horizontal, upward-facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

12. **Quick stick (peel tack) test:** In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required breaking the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

13. **Probe tack test:** In this test, the tip of a clean probe with 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 a fixed rate is recorded as a tack and it is expressed in grams.

14. *In-vitro* drug release studies: The paddle over disc method (USP apparatus 5) is employed to assess the release of 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 500 ml of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus is equilibrated to 32 ± 0.5ºC. The magnetic bead was kept at a speed of 50 rpm. Samples (2 ml aliquots) can be withdrawn at appropriate time intervals up to 6h and analyzed by UV spectrophotometer.

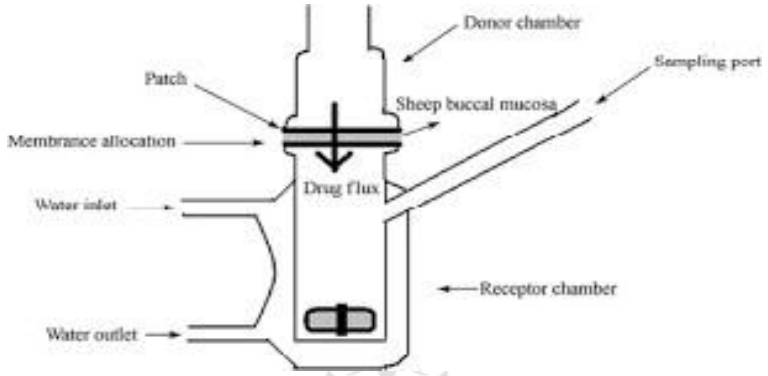

Figure No. 7: Assembly of Diffusion Cell

The cell used for the diffusion process was the Franz diffusion cell. The cell consists of: 1) Donor compartment 2) Receptor compartment.[16, 17, 18, 19]

CONCLUSION:

The transdermal drug delivery patch is a painless, convenient, and potentially effective way to deliver regular doses of many medications. It is used to overcome the difficulties of drug delivery through the oral route. The number of drugs that can be delivered increases drug uptake, reduces complications and side effects, low cost, and easy to use. The transdermal patch provides a controlled release of the medication. This article provides valuable information regarding the types, basic components, methods of preparation, and evaluation of transdermal patch as a ready reference for the research scientists who are involved in TDDS.

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