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Approaches and evaluation of Transdermal drug delivery system

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Abstract:

Conventional dosage form have significant setbacks of poor bioavailability and frequent dosing due to hepatic first pass metabolism. Continuous intravenous infusion at a programmed rate has been recognised as a superior mode of drug delivery not only to bypass hepatic metabolism but also to maintain a constant concentration in blood for prolonged period in therapeutic range. However such a mode of drug delivery has certain risks and necessitates hospitalization and close medical supervision. Recently there has been an increasing awareness that the benefits of IV drug infusion can be closely duplicated without its potential hazards, by continuous transdermal drug administration through intact skin.

INTRODUCTION

Transdermal therapeutic system are defined as self contained, discrete dosage form which when applied to intact skin deliver the drug through the intact skin at a control rate to the systemic circulation and maintain the drug concentration within the therapeutic window for prolonged period of time. Recently, the use of transdermal patches for pharmaceuticals is limited because only a few drugs has proven to be effectively delivered through skin. in order to achieve the objective of systemic medication through topical application to the intact skin surface. They were exemplifies first with the development of a scopolamine-releasing TDD system (Transderm-scop) for 72 hrs for prophylaxis or treatment of motion-induced nausea, then by the successful marketing of nitroglycrine-releasing TDD system (Deponit, Nitrodisc, nitro-dur,transderm-nitro).

Transdermal patch uses a special membrane to control the release rate at which the liquid drug contained patch reservoir can pass through the skin and itno the blood stream. Transdermal delivery not only provide controlled,constant administration of the drug, but also allows continuous input of drugs with short biological half lives, and eliminates pulsed delivery into systemic circulation which is responsible for undesirable side effects[1].

ADVANTAGES[2,3]

- Transdermal medication delivers a steady infusion of the drug over prolonged period of time therefore avoiding adverse side effects and therapeutic failure frequently associated with intermittent dosing can also be avoided.
- Alternative route of administration for the patients who cannot tolerate oral dosage forms such as vomiting patient.
- Increases therapeutic value of many drugs by avoiding specific problems associated with

the drug e.g., gastro-intestinal irritation, low absorption and drug interaction with food, drink and other administered drugs.

- Avoidance of first pass metabolism because it bypasses the liver.
- Simplified regimen leads to improved patient compliance and reduced inter and intra-patient variability.
- Self administration is possible and they are non invasive, avoiding the inconvenience of parenteral therapy.
- Drug input can be terminated at any point of time by removing the transdermal patch.
- They are easily and rapidly identified in emergencies (for example, unresponsive, unconscious or comatose patient) because of their physical presence, features and identifying markings.

At the same time transdermal drug delivery has few disadvantages that are limiting the use transdermal delivery.

DISADVANTAGES[2,3]

- Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability[22].
- Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
- The delivery system cannot be used for drugs requiring high blood levels[22].
- The use of transdermal delivery may be uneconomical.

Table 1: Marketed Products of Transdermal Drug Delivery System ([4,5,6])

S. No	PRODUCT	ACTIVE DRUG	TYPE OF PATCH	PURPOSE
1	Estraderm	Estradiol	Membrane	Postmenstrual syndrome
2	Duragesic	Fentanyl	Reservoir	Pain relief patch
3	Transderm-scop	Scopolamine	Matrix	Motion sickness
4	Deponit	Nitroglycrine	Drug in adhesive	Angina pectoris
5	Lidoderm	Lidocaine	Drug in adhesive	Anaesthetic
6	Testoderm TTS	Testosterone	Reservoir	Hypogonadism in males
7	Fematrix	Estrogen	Matrix	Postmenstrual syndrome
8	Nitrodur	Nitroglycrine	Matrix	Angina pectoris

For better understanding of transdermal drug delivery, the structure of skin should be briefly discussed along with penetration through skin and permeation pathways.

Anatomy and physiology of skin[1]

Skin is one of the most extensive organ of the body covering an area of about $2m^2$ on in an average human adult. This multilayerd organ receives approximately one third of all blood circulating through the body. With thickness of only a millimeter, the skin separates the underlying blood circulation network from outside environment.

Human skin comprises of three distinct but mutually dependent tissues:

A) The stratified, vascular, cellular epidermis,

B) Underlying dermis of connective tissues and

C) Hypodermis.

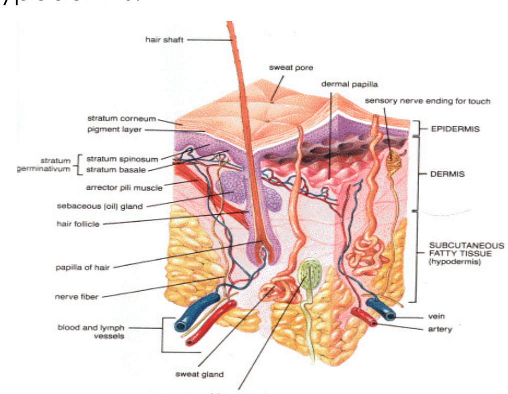


Figure: Structure of skin Epidermis[16]

Epidermis: it results from an active epithelial basal cell population and is approximately 150 micrometer thick. It is the outermost layer of skin and process of differentiation results in migration of cells from basal layer towards the skin surface. The end result of this process is the formation of a thin, stratified and extremely resilient layer(the stratum corneum) at the skin surface.

Stratum corneum: This is the outermost layer of skin, also called horny layer. It is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of parallel to the skin surface, lying dead, keratinized cells, called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration. The barrier nature of the horney layer depends critically on its constituents: 75 to 80% proteins, 5 to 15% lipids, and 5 to 10% ondansetron material on a dry weight basis. Protein fractions predominantly contain alpha-keratin (70%) with some beta-keratin (10%) and cell envelope (5%). Lipid constituents vary with body site (neutral lipids, sphingolipids, polar lipids, cholesterol). Phospholipids are largely absent, a unique feature of mammalian membrane.

Viable epidermis: This is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms.

Dermis: electron microscopic examination shows that the dermis is made up of a network of robust collagen fibers of fairly uniform thickness with regularly spaced cross striations.

It is about 3 to 5 mm and contains the blood vessels, lymph vessels, and nerves. It also provide oxygen and nutrients to the skin while removing toxins and waste products.

Hypodermis: The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanic protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery, only penetration through stratum corneum is essential and then retention of drug in skin layers is desired.

Route of Permeation of Skin[2,19]:

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

Transcorneal penetration

Intra cellular penetration[19]

Drug molecule passes through the cells of the stratum corneum. It is generally seen in 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.

Intercellular penetration[19]

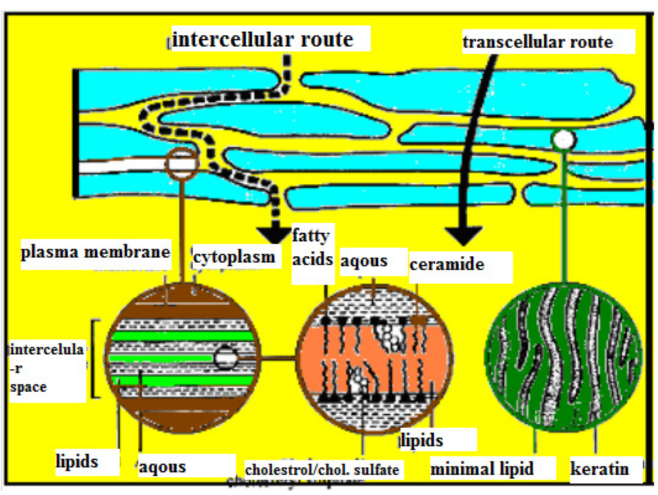
Non-polar substances follow the route of intercellular penetration. These molecules dissolve in and diffuse through the non- aqueous lipid matrix imbibed between the protein filaments.

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 transappendegeal 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 importantantly being the relative ability to partition into each skin phase. The transdermal permeation can be visualized as 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 through 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 like a passive diffusion medium. So for transdermal drug diffusion, the various skin tissue layers can be represented by a simple multilayer model as shown in Figure.



Epidermal route for drug permeation

Kinetics of transdermal permeation[2]

Knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic system. Transdermal permeation involves following steps:

- Sorption by stratum corneum,
- Penetration of drug through viable epidermis,
- Uptake of the drug by capillary network in dermal papillary layer.

This permeation is possible only if drug posses certain physicochemical properties. The rate of permeation across the skin(dQ/dt) is given by

$$\frac{dQ}{dt} = P_s(C_d - C_r) \rightarrow (1)$$

Where C_d and C_r are the concentrations of the skin penetrant in the donor compartment(e.g, on the surface of stratum corneum) and in the receptor compartment(e.g, body) respectively P_s is the overall permeability coefficient of the skin tissue to the penetrant and is given by

$$P_s = \frac{K_s}{h_s} \times D_{ss}$$

Where K_s is the partition coefficient for the interfacial partitioning of the penetrant molecule form a transdermal therapeutic system on to the stratum corneum, D_{ss} is the apparent diffusivity for the steady state diffusion of the molecule through a thickness h_s of the skin tissue. As the k_s, D_{ss}, h_s are constant under given condition, the permeability coefficient(p_s) for a skin penetrant can be considered to be a constant.

Now it is clear that a constant rate of drug permeation can be obtained only when $C_d >> C_r$ i.e, the drug concentration at the stratum corneum(C_d) is consistently greater than the concentration in the body(C_r) , then equation one becomes:

$$\frac{dQ}{dt} = P_s \times C_d$$

The rate of skin permeation(dQ/dt) is constant provided the magnitude of C_d remains fairly constant throughout the course of skin permeation. For keeping C_d constant, the drug should be released from the device at a rate (R_r) that is either constant or greater than the rate of skin uptake(R_a) i.e., $R_r >> R_a$

Since ., R_r is greater than R_a, the drug concentration on the skin surface(C_d) is maintained at a level equal to or greater than the equilibrium(or saturation) solubility of the drug in stratum corneum(C_s) i.e., $C_d >> C_s$ .therefore maximum rate of skin permeation[$(dQ/dt)_m$] is given by equation:

$$(dQ/dt)_m = P_s \times C_s$$

From the above equation, it can be seen that the maximum rate of skin permeation depends on the skin permeability coefficient(P_s) and its equilibrium solubility in the stratum corneum(C_s). Thus skin permeation appears to be stratum corneum limited.

Basic Components of Transdermal Drug Delivery Systems[2]:

- Polymer matrix or matrices
- The Drug
- Permeation enhancers
- Other excipients

Polymer matrix[1,2,20]:

Advances in transdermal drug delivery technology have been rapid because of the sophistication of polymer science that now allows incorporation of polymers in transdermal system (TDS) in adequate quantity. The release rate from TDS can be tailored by varying polymer composition. Selection of polymeric membrane is very important in designing a variety of membrane permeation controlled TDS. The following criteria should be satisfied for a polymer to be used in a transdermal system:

- Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
- Polymer should be stable, non-reactive with the drug, easily manufactured and fabricated into the desired product and inexpensive.
- Polymer and its degradation product must be non-toxic or non-antagonistic to the host.

The mechanical properties of the drug the polymer should not deteriorate excessively when large amount of active agents are incorporated into it.

Polymer useful for transdermal devices

S. No	Polymer	Category	Role
1	Gelatin	Natural	Base, adhesive
2	Na-alginate	Natural	Base, adhesive
3	Gum Arabic	Natural	Base with adhesive
4	Gum tragacanth	Natural	Adhesive
5	Carmellose	Semi synthetic	Base, adhesive
6	Methyl and ethyl cellulose	Semi synthetic	Base, adhesive
7	Hydroxy propyl cellulose	Semi synthetic	Base, adhesive
8	Polyvinyl alcohol	Synthetic	Base, adhesive
9	Polyethylene	Synthetic	Liner, backing
10	Polypropylene	Synthetic	Membrane, liner
11	Polyvinyl chloride	Synthetic	Base, adhesive
12	Ethylene vinyl acetate	Synthetic	Membrane
13	Polystyrene	Synthetic	Co-adhesive

DRUG[1]:

For successfully developing the transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of drug for transdermal drug delivery:

Physicochemical properties

1. The drug should have a molecular weight less than approximately 1000 Daltons;

2. The drug should have affinity for both-lipophilic and hydrophilic phases. Extreme partitioning characteristic are not conducive to successful drug delivery via the skin;
3. The drug should have a low melting point usually below 200℃
4. Since the skin has pH of 4.2 to 5.6, solutions which have this pH range are used to avoid damage to the skin. However for a number of drugs, there may also be significant transdermal absorption at pH values at which the unionized form of the drug is predominant.

Biological properties

1. The drug should be potent with a daily dose of the order of a few mg/day;
2. The half life t½ of the drug should be short;
3. The drug should be non-irritating and non allergic;
4. Drugs which degrade in the gastro intestinal (GI) tract or inactivated by hepatic first-pass effect are suitable candidates for transdermal delivery.

Permeation enhancers[2]:

These are the compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant.

$$j = D \times \frac{dc}{dx}$$

Where D is the diffusion coefficient and is a function of size, shape and felxibilty of the diffusing molecule as well as the membrane resistance, c is the concentration of the diffusing molecule and x is the spatial coordinate.

Thus enhancement of flux across membranes reduces to considerations of:

- Thermodynamics(lattice energies, distribution coefficient)
- Molecular size and shape.
- Reducing the energy required to make a molecular hole in the membrane

Permeation enhancer are hypothesized to affect structure of proteins and lipids therefore altering the barrier energy to hole formation.

Chemical approach[3,17]:

This includes:

(a) Synthesis of lipophilic analogs;
(b) Delipidization of stratum corneum;
(c) Co-administration of skin permeation enhancers.

This chemical approach can further be classified according to their chemical class;

(i) Sulfoxides: Dimethyl sulfoxide, decylmethal sufoxide;
(ii) Alcohols: Ethanol;
(iii) Polyols: Propylene glycol;
(iv) Alkenes: Long chain alkanes (C7-C16);
(v) Fatty acids: oleic acid;
(vi) Esters: Isopropyl myristate;
(vii) Amines and amides: Urea, dimethyl acetamide, dimethyl formamide;
(viii) Pyrrilidones: N-methylpyrrilidone, azones;
(ix) Terpenes: Eugenol;
(x) Surface active agents: Cationic surfactants;
(xi) Cyclodextrines.

Biochemical approach

This includes:

(a) Synthesis of bio-convertible pro-drugs and;
(b) Co-administration of skin metabolism inhibitors.

Physical approach

This includes:

(a) Iontophoresis;
(b) Sonophoresis: Ultrasonic energy;
(c) Thermal energy;
(d) Stripping of stratum corneum and;
(e) Hydration of stratum corneum.

Adhesive layer[7,8,9]:

The adhesive must posses' sufficient property so as to firmly secure the system to the skin surface and to maintain it in position for as long as desired, even in the presence of water. After removal of patch, any traces of adhesive left behind must be capable of being washed with water and soap. Pressure sensitive adhesives are used to achieve contact between the transdermal patch and the skin. Adhesion is understood to be the net effect of three phenomenon's namely;

1. Peel: The resistance against the breakage of the adhesive bond;
2. Track: The ability of a polymer to adhere to a substrate with little contact Pressure and;
3. Creep: The viscous relaxation of the adhesive bond upon shear.

The ideal characters of adhesive materials are (Qvist et al., 2002);

1. High biocompatibility (low irritancy, toxicity, allergic reaction etc.);
2. Good adhesive to oily, wet, wrinkled and hairy skin;
3. Good environment resistance against water and humidity;
4. Easy to remove from the skin;
5. High permeability of moisture to avoid excessive occlusion and for the drug itself and;
6. Non-reactive towards drug.

There are three types of adhesive used mainly (Qvist et al., 2002; Govil et al., 1993);

1. Silicone type adhesive;
2. Polyisobutylene adhesive and;
3. Polyacrylate based adhesive.

Backing layer[8]:

The backing layer must be impermeable to drug and permeation enhancers. The backing membrane serves the purpose of holding the entire system together and at the same time protects the drug reservoir from exposure to the atmosphere, which could result in the breakage or loss of the drug by volatilization. The most commonly used backing materials are polyester, aluminized polyethylene terapthalate, siliconised polyethylene.

Release liner:

The peel strip prevents the loss of the drug that has migrated into the adhesive layer during storage and protects the finished device against contamination. Polyesters foils and other metalized laminates are typical materials which are commonly used.

Ideal properties of transdermal drug delivery system:

- Shelf life should be upto to 2.5 years
- Patch size should be less than 40 cm^2
- Dose frequency once a daily-once a week
- Should be clear or white color
- Should be non-irritating to the skin
- Release properties- should have consistent pharmacokinetic and pharmacodynamic profile over the time

Types of transdermal drug delivery system[1]:

Polymer membrane permeation controlled TDD system: Drug reservoir sandwiched between drug impermeable backing laminate and rate controlling polymeric membrane. In drug reservoir compartment drug is dispersed homogeneously in a solid polymeric matrix(e.g. polyisobutylene), suspended in a unleachable viscous liquid medium(e.g. silicon fluid) to form a paste like suspension. Rate controlling membrane is either a microporous or a nonporous polymeric membrane e.g. ethylene-vinyl acetate copolymer. example of this type of patch are Estraderm(twice a week in treatment of postmenopausal syndrome) and

Duragesic(management of chronic pain for 72 hrs).

Polymer matrix diffusion controlled TDD system: Drug reservoir is formed by homogeneously dispersing the drug solids in hydrophilic or lipophillic matrix and the medicated polymer formed is than molded into medicated disk with defined surface area nd controlled thickness. e.g. Nitro-dur system once-a-day medication for angina pectoris.

Drug reservoir gradient controlled TDD system: To overcome nonzero order drug release profile from polymer matrix TDD system can be modified to have drug loading level varied in increamental manner forming a gradient of drug reservoir along the diffusional path across the multilaminate adhesive layer. e.g. Deponit system

Microreservoir dissolution controlled TDD system: considered as the hybrid systemof reservoir and matrix dispersion type drug delivery. In this system the drug reservoir is formed by first suspending the drug solids in aqous solution of water-miscible drug solubilser e.g. polyethylene glycol and than homogeneously dispersing the drug suspension with controlled aqous soluble lipophillic polymer by high shear mechanical force to form thousands of unleachable microscopic drug reservoir.

Evaluation parameters:

1. Thickness of the patch[4,11]: The thickness of the drug loaded patch is measured in different points by using a digital micrometer and the average thickness and standard deviation is determined to ensure the thickness of the prepared patch. The thickness of transdermal film is determined by travelling microscope dial gauge, screw gauge or micrometer at different points of the film.

2. Weight uniformity[11]: The prepared patches are dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

3. Folding endurance[12]: A strip of specific area is to be cut evenly and 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.

4. Percentage Moisture content[10,11]: 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.

$$\%\,Moisture\ content = \frac{(initial\ weight - final\ weight)}{final\ weight} \times 100$$

5. Content uniformity test[4,10]: 10 patches are selected and content is determined for individual patches. If 9 out of 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. Moisture Uptake[4,11]: Weighed films are kept in desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. % moisture uptake is calculated as given below.

$$\%\,Moisture\ upatke = \frac{final\ weight - initial\ weight}{initial\ weight} \times 100$$

7. Drug content[4,12]: 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.

8. Shear Adhesion test[13]: This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross linking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength.

9. Peel Adhesion test[13]: In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180° angle, and the force required for tape removed is measured.

10. Water vapor transmission studies (WVT)[14]: 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 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.

$$WVT = \frac{W}{ST}$$

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

11. Rolling ball tack test[5]: This test measures the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

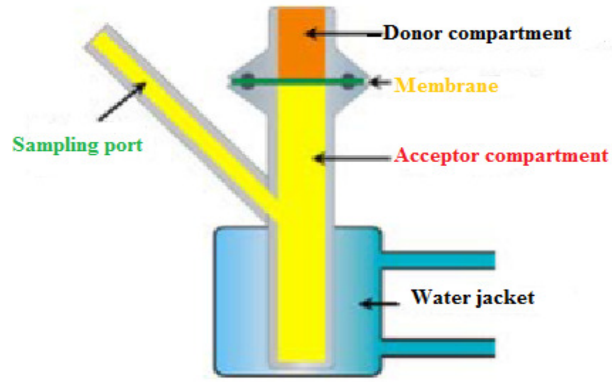
12. Quick Stick (peel-tack) test[5]: In this test, the tape is pulled away from the substrate at 90°C at a speed of 12 inches/min. The peel force required breaking the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

13. Probe Tack test[5]: In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.

14. In vitro drug release studies[6]:

The paddle over disc 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 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus is equilibrated to 32± 0.5°C. The paddle is then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5- mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

15. In vitro skin permeation studies[6,21]: An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Westar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin is thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and is placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell is maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample 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. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm-2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm-2).



Tran's diffusion cell

16. Skin Irritation study[13]: Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

17. Stability studies[6]: Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months. The samples are withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.

THE FUTURE[2]:

The future development of transdermal therapeutic system is multifaceted. Improvement in the presently available devices to provide optimum blood levels, availability of better skin permeability enhancers and extensive use of redesigned drug molecules (prodrugs) and novel formulation approaches include liposomes, niosomes and microemulsions are some of the aspects envisioned. The market for transdermal devices has been estimated to increase in future and has recently experienced annual growth of at rate of 25%. This figure will rise in future as novel devices emerge and list of marketed transdermal drug increases. Transdermal delivery of analgesics is likely to continue to increase in popularity as there are further improvements in design. Research is being performed to increase safety and efficacy. To improve practical matters such as the experience for the wearer of the patch, and also to provide more precise drug delivery associated with increased duration of action. Other potential improvements include improved transdermal technology that utilizes mechanical energy to increase drug flux across the skin either by altering the skin barrier or increasing the energy of the drug molecules. After the successful design of patches using iontophoresis, various modes of 'active' transdermal technologies are being investigated for different drugs. These include electroporation (short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (uses low-frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (uses heat to make the skin more permeable and to increase the energy of drug molecules).

Conclusion[2]:

Due to recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin, membrane trasdermal route is effective. The transdermal durg delivery system has been designed as an alternative, safest, and easy route for systemic drug delivery. It has been used as safe and effective drug delivery devices since 1981. Due to large advantages of the Transdermal Drug Delivery System, this system interests a lot of researchers. Many new researches are going on in the present day to incorporate newer drugs via this system. Transdermal dosage forms may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care. Transdermal drug therapy will revolutionalize the concept of "dose" of drug to be administered. No longer will physicians prescribe a certain "dose" of a drug, but will prescribe drugs to be given at a certain "rate". Transdermal systems will be designed to give variable rates with variable areas thus TDDS may be very usefull in the treatment of chronic disorders such as hypertension, diabetes mellitus and many more.

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