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Review Article

A Comprehensive Review on: Transdermal drug delivery systems

Kharat Rekha Sudam* and Bathe Ritesh Suresh

Department of Pharmaceutics, Sahyadri College of Pharmacy, Methwade, Sangola-413307, Solapur, Maharashtra, India

***Correspondence Info:**
Kharat Rekha Sudam
Department of Pharmaceutics,
Sahyadri College of Pharmacy, Methwade,
Sangola-413307, Solapur, Maharashtra, India
E-mail: kharatrs26@gmail.com

Abstract

Transdermal drug delivery system was introduced to overcome the difficulties of drug delivery through oral route. Despite their relatively higher costs, transdermal delivery systems have proved advantageous for delivery of selected drugs, such as estrogens, testosterone, clonidine and nitro-glycerine. Transdermal delivery provides a leading edge over injectable and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. Skin is an effective medium from which absorption of the drug takes place and enters into systematic circulation over a period of time. The present article reviews the selection of drug candidates and polymers suitable to be formulated as transdermal system, advantages, disadvantages of formulation design and the methods of evaluation.

Keywords: Transdermal drug delivery systems (TDDS)**,** World Health Organization (WHO), Penetration enhancer, Cardiovascular

1. Introduction

Transdermal drug delivery system was first introduced more than 20 years ago. The technology generated tremendous excitement and interest amongst major pharmaceutical companies in the 1980s and 90s. By the mid to late 1990s, the trend of Transdermal drug delivery system companies merging into larger organizations.

More recently, such dosage forms have been developed and/or modified in order to enhance the driving force of drug diffusion (thermodynamic activity) and/or increase the permeability of the skin. These approaches include the use of penetration enhancers, supersaturated systems, hyaluronic acid, pro-drugs, liposome's and other vesicles.

Innovations in technologies continue to occur at a positive rate, making the technology a fertile and vibrant area of innovation, research and product development. Transdermal drug technology specialists are continuing to search for new methods that can effectively and painlessly deliver larger molecules in therapeutic quantities to overcome the difficulties associated with the oral route. Transdermal Drug Delivery System is the system in which the delivery of the active ingredients of the drug occurs by the means of skin. Skin is an effective medium from which absorption of the drug takes place and enters the circulatory system.

Various types of Transdermal patches are used to incorporate the active ingredients into the circulatory system via skin. The patches have been proved effective because of its large advantages over other controlled drug delivery systems. This review article covers a brief outline of various components of Transdermal patch, applications of Transdermal patch, their advantages, disadvantages, when the Transdermal patch are used and when their use should be avoid and some of the recent development in the field along with the latest patents in this field.

A Transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication.

Today drugs administered through skin patches include scopolamine (for motion sickness), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), and lidocaine to relieve the pain of shingles (herpes zoster). Non-medicated patches include thermal and cold patches, weight loss patches, nutrient patches, skin care patches (therapeutic and cosmetic), and aroma patches, and patches that measure sunlight exposure.

A transdermal patch is defined as adhesive medicated patch that is placed on to the above skin to deliver an exact dose of drug through the skin into the bloodstream with a predetermined rate of release to reach in the body. Today the most common transdermal system present in the market mainly based on semi permeable membranes which

were called as patches. Transdermal drug delivery systems (TDDS), also known as "**Transdermal patches**" or "**Skin patches**" are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin and in the bloodstream.

Transdermal drug delivery system has been in existence for a long time. Cardiovascular/ Antihypertensive diseases are the major concern of death in India. Cardiovascular diseases (CVD) are the cause of more than 30% of deaths, not only in the developed countries. The World Health Organization (WHO) estimates that low- and middle income countries are disproportionately affected. 82% of CVD deaths take place in low- and middle-income countries and occur almost equally in men and women. In order to deliver therapeutic agents through the human skin for systemic effects of the Cardiovascular/Antihypertensive diseases, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. [1]

Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. Recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven to be effectively delivered through the skin, typically cardiac drugs such as nitroglycerin and hormones such as estrogen. A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. [2] Transdermal drug delivery system [TDDS] is a new approach to provide prolonged action of the drug with low toxicity and better patient compliance and thus reduces the side effect caused by oral route. Transdermal drug delivery system is the integral part of novel drug delivery system. It is defined as self-contained discrete dosage form which when applied trans-dermally provides systemic circulation at controlled rate. [3]

For effective Transdermal drug delivery system, the drugs are easily able to penetrate the skin and easily reach the target site. TDDS increase the patient compliance and reduces the load as compared to oral route. Transdermal formulation maintain drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration. [4]

2. Advantages of TDDS:[5]

1) They avoid the first-pass effect, that is, the initial passage of "s" drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzymes.
2) Self-administration medicament.
3) Increase bioavailability.
4) Reduce dosing frequency.
5) Transdermal drug delivery can be used as an alternative route of administration to accommodate patients who cannot tolerate oral dosage forms.
6) It is of great advantage in patients who are nauseated or unconscious.
7) Drugs that require relatively consistent plasma levels are very good candidates for transdermal drug delivery.
8) Maintains stable or constant and controlled blood levels for longer period of time.
9) The daily dose of the drug required is lower than that with conventional therapies.
10) The drug release is such that there is a predictable and extended duration of activity.
11) Drug therapy may be terminated rapidly by removal of its application from the surface of the skin.
12) They are easily and rapidly identified in emergencies (for example, unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings.

3. Disadvantages of TDDS:[6-8]

1) Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
2) Higher cost.
3) Should not use ionic drug.
4) May cause allergic reactions.
5) A molecular weight less than 500 Da is essential.
6) Sufficient aqueous and lipid solubility, a log P (octanol/water) between 1 and 3 is required for permeate to transverse SC and underlying aqueous layers.
7) Transdermal therapy is feasible for certain potent drugs only.
8) Transdermal therapy is not feasible for ionic drugs.
9) It cannot deliver drug in pulsatile fashion.
10) Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.

4. Limitations of TDDS:

1) Limited skin permeability.
2) Restricted to potent drug
3) Cannot use for large molecule (>500 Dalton)
4) Significant lag time
5) Difficulty for adhesion.
6) The drug undergoes degradation in the skin.
7) Variation in absorption efficiency at different sites of skin.

5. Ideal Characteristics of TDDS: [9]

1) The skin has pH of 4.2 to 5.6, solutions which have this pH range are used to avoid damage to the skin.
2) For the therapeutic action of the drug, there is a need of optimum partition coefficient.
3) The drug should have a low melting point (less than 200^0C) should use.
4) Patch size should be less than 40 cm^2
5) Shelf life upto 2 yrs.
6) The half-life t½ of the drug should be short;
7) The drug should be non-irritating and non-allergic;
8) The drug should be potent with a daily dose of the order of a few mg/day;
9) The drug should have a molecular weight less than approximately 1000 Daltons;
10) The drug should have affinity for both-lipophilic and hydrophilic phases. Extreme partitioning characteristic are not conducive to successful drug delivery via the skin;
11) 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.

5. Conditions in which Transdermal patches are used:

Transdermal patch is used when:

1) When the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery.
2) Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia.
3) It can be used in combination with other enhancement strategies to produce synergistic effects.

6. Anatomy and physiology of skin:[10-11]

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.

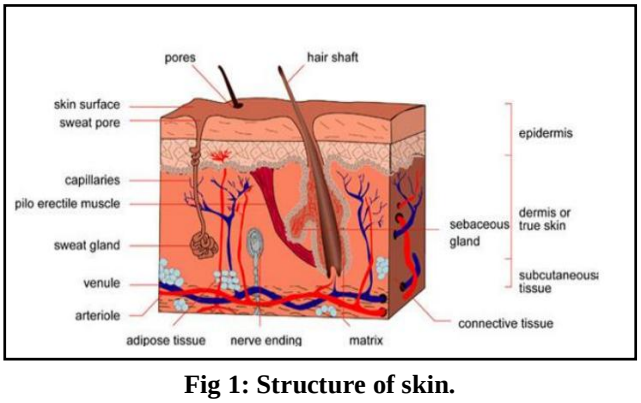

Fig 1: Structure of skin.

A. Epidermis:

The multilayered epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Table 1 gives thickness, water permeability and diffusivity of water through epidermis. It consists outer stratum corneum and viable epidermis.

1) Horney layer (Stratum corneum):

This is the outermost layer of skin also called as horney layer. It is approximately 10 µm thick when dry, but swells to several times this thickness when fully hydrated. It has 10 to 30 layers of dead, keratinized cells called corneocytes.

There are three possible ways that drug molecules can pass through stratum corneum. The drug can be absorbed by various pathways through the skin depending on the physicochemical properties of the drug. Both lipophilic and hydrophilic drugs are absorbed from different routes.

a) Transfollicular route:
b) Transcellular route:
c) Intercellular route:

2) Viable epidermis:

This is situated beneath the outermost layer and varies in thickness ranging from 0.06 mm on the eyelids sole upto 0.8 mm on the palms. Going inwards, it consists of various layers as stratum granulosum, stratum lucidum, stratum spinosum and the stratum basal. In the basal layer, mitosis divisions of the cells constantly reproduce the epidermis and this proliferation compensates the loss of dead horney cells from the skin surface.

B. Dermis:

Dermis is 3 to 5mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of a permeant very low and the resulting concentration difference across the epidermis provides the essential concentration gradient for transdermal permeation.

C. 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 al protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs.

7. Drug permeation pathway:

Percutaneous absorption involves passive diffusion of the substances through the skin A molecule may use two

diffusional routes to penetrate normal intact skin, the appendageal route and the epidermal route.

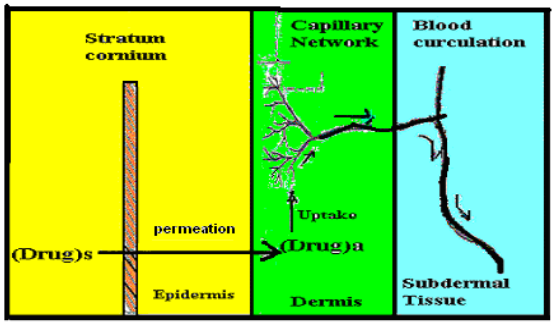

Fig 2: Multilayer skin model showing sequence of Transdermal permeation of drug for systemic delivery.

There are critically three ways in which a drug molecule can cross the intact stratum corneum: via skin appendages (shunt routes); through the intercellular lipid domains; or by a transcellular route (Figure 3).

Appendageal route (shunt route)

- Epidermal
- Transcellular.
- Paracellular

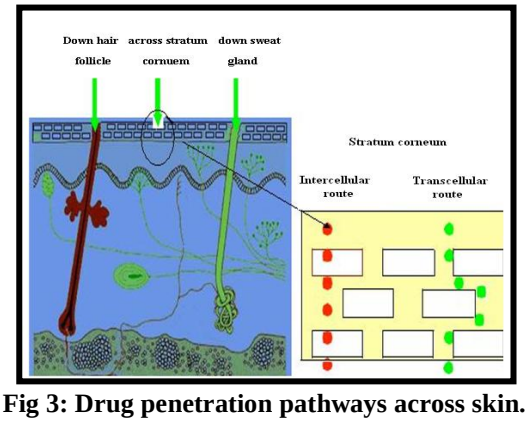

Fig 3: Drug penetration pathways across skin.

❖ **Appendageal route:**

Appendageal route comprises transport via sweat glands and hair follicles with their associated sebaceous glands. These routes circumvent penetration through the stratum corneum and are therefore known as "shunt" routes. This route is considered tobe of minor importance because of its relatively small area, approximately 0.1 % of the total skin area.

❖ **Epidermal route:**

1) Transcellular:

Pathway means transport of molecules across epithelial cellularmembrane. These include passive transport of small molecules, active transport of ionic and polarcompounds and endocytosis and transcytosis of macromolecules.

2) Paracellular:

Paracellular pathway means transport of molecules around or between the cells. Tight junctions or similar situations exist between the cells. The principal pathway taken by a permeant is decided mainly by the partition coefficient (log k). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophilic permeants traverse the stratum corneum via the intercellular route. Most permeants permeate the stratum corneum by both routes. However, the tortuous intercellular pathway is widely considered to provide the principal route and major barrier to the permeation of most the drugs.

Types of Transdermal Drug delivery systems: [12]

There are four types of transdermal patches:

(I) Single–layer drug in–adhesive:

The adhesive layer of this system also contains the drug. In this type patches the adhesive layer not only serves to adhere the various layer together, along with entire system to the skin but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

Fig. 4: Single–layer drug in–adhesive

(II)Multi-layer drug in adhesive

The multi-layer drug in adhesive is similar to the single layer system in that both adhesive layer are also responsible for the releasing of the drug. But it is different however that it adds another layer of drug in–adhesive, usually separated by a membrane. This patch also has a temporary liner–layer and a permanent backing.

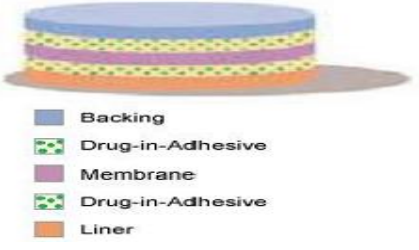

Fig. 5: Multi–layer drug in–adhesive.

(III) Drug reservoir-in-adhesive: Reservoir

Transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the backing layer. In this type of system the rate of release is zero order.

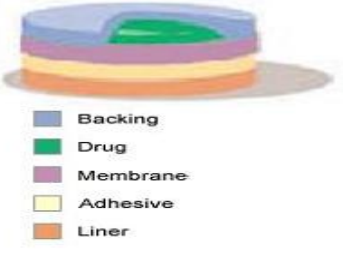

Fig. 6: Drug reservoir-in-adhesive

(IV) Drug Matrix-in-adhesive

This matrix system has a drug layer of semisolid matrix containing a drug solution or suspension. The

adhesive layer in this patch surrounds the drug layer partially overlaying it.

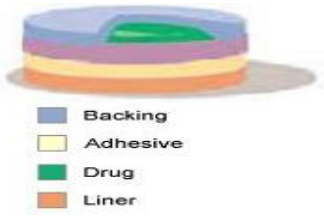

Fig. 7: Drug Matrix-in-adhesive.

8. Formulation Design: [13-17]

A transdermal therapeutic system is essentially a multilaminate structure that is composed of following constituents:

1. Drug;
2. Polymer matrix;
3. Penetration enhancers;
4. Adhesives;
5. Backing membrane;
6. Release linear.

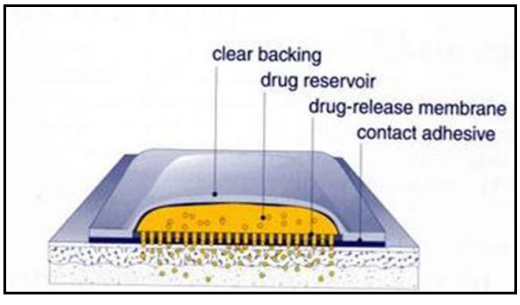

Fig. 9: Different layers of transdermal patches

Drug:

Transdermal route of administration cannot be employed for all types of drugs. It depends upon optimal physicochemical properties of the drug, its biological properties. In addition, consideration of the pharmacokinetic and pharmaco-dynamic properties of drug is necessary. The most important requirement of drug to be delivered trans-dermally is demonstrated by need for controlled delivery, such as short half-life, adverse effect associated with other route or a complex oral or I.V. dose regimen. The drug parameter required for ideal drug candidate for transdermal drug delivery as above:

Polymer:

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 criteria for the polymers are:

1) The polymer should be chemically non-reactive or it should be an inert drug carrier;
2) The polymer must not decompose on storage or during the life span;
3) Molecular weight, physical characteristic and chemical functionality of the polymer must allow the diffusion of the drug substance at desirable rate;
4) The polymer and its decomposed product should be nontoxic. It should be biocompatible with skin;
5) The polymer must be easy to manufacture and fabricate into desired product. It should allow incorporation of large amounts of active agent.

Penetration enhancer

To increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug penetration enhancers interact with structural components of stratum corneum i.e. proteins or lipids. The enhancement in absorption of oil soluble drugs is apparently due to the partial leaching of the epidermal lipids by the chemical enhancers, resulting in the improvement of the skin conditions for wetting and for transepidermal and transfollicular penetration. The miscibility and solution properties of the enhancers used could be responsible for the enhanced transdermal permeation of water soluble drugs. Pharmaceutical scientists have made great efforts in transdermal permeation studies using various enhancers for several drug moieties. Sorption promotes act by interaction with intracellular lipids leading to disrtruption of their organization and increasing their fluidity. Some of them also interact with intercellular protein, keratin denaturation (azone and oleic acid) while others act by both mechanism (DMSO and propylene glycol). Another possible mechanism is by altering the skin hydration.

Ideal penetration enhancers should possess the following properties:

1. They should be non-toxic, non-irritating and non-allergic.
2. They would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible.
3. They should have no pharmacological activity within the body.
4. The penetration enhancers should work uni-directionally, i.e., they should allow therapeutic agents into the body whilst preventing the loss of endogenous materials from the body.
5. When removed from the skin, barrier properties should return both rapidly and fully to normal.
6. They should be cosmetically acceptable with an appropriate skin feel.
7. Pharmacologically inert.

Adhesive layer

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:

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

1. Silicone type adhesive;
2. Poly-isobutylene adhesive and;
3. Poly-acrylate based adhesive.

Backing layer

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 poly-ethylene terapthalate, siliconised polyethylene terapthalate and aluminum foil of metalized polyester laminated with 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.

10. Factors affecting transdermal permeation: [18,19]

Physicochemical properties of the penetrant molecules:

A. Partition coefficient

- A lipid/water partition coefficient of 1 or greater is generally required for optimal transdermal permeability.
- It may be altered by chemical modification without affecting the pharmacological activity of the drug.

B. pH conditions

- Applications of solutions whose pH values are very high or very low can be destructive to the drug.
- With moderate pH values, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability.

C. Penetrant concentration

- Assuming membrane related transport, increasing concentration of dissolved drug causes a proportional increase in flux.
- At concentration higher than the solubility, excess solid drug functions as a reservoir and helps maintain a constant drug constitution for a prolonged period of time.

Physicochemical properties of the drug delivery system

A. Release characteristics

Solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depends on the following factors:

- Whether the drug molecules are dissolved or suspended in the delivery systems.
- The interfacial partition coefficient of the drug from the delivery system to the skin tissue.
- pH of the vehicle

B. Composition of the drug delivery systems

The composition of the drug delivery systems e.g., boundary layers, thickness, polymers, vehicles not only affects the rate of drug release, but also the permeability of the stratum corneum by means of hydration, making with skin lipids, or other sorption promoting effects e.g., benzocaine permeation decreases with PEG of low molecular weight.

Approaches or Technologies used in Development of Transdermal Patch: [20-22]

The technologies can be classified in four basic approaches:

Polymer membrane partition-controlled TDD systems

In this type of systems, the drug reservoir is sandwiched between a drug-impermeable backing laminate and a rate controlling polymeric membrane.

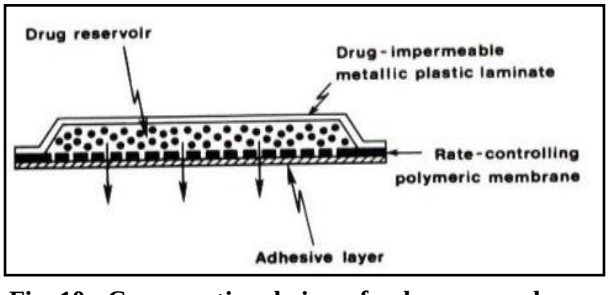

Fig. 10: Cross-sectional view of polymer membrane permeation-controlled TDD systems.

The drug is allowed to permeate only through the rate controlling membrane. The drug solids are homogeneously dispersed in a solid polymer matrix, suspended in an unleachable, viscous liquid medium e.g. silicone fluid to form a paste like suspension or dissolved in a releasable solvent e.g. alkyl alcohol to a clear drug solution. The rate controlling membrane can be either a micro-porous or a nonporous polymeric membrane e.g. ethylene-vinyl acetate copolymer, with specific drug permeability. On the external surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic pressure sensitive adhesive

polymer e.g. silicone adhesive may be applied to provide intimate contact of TDDS with the skin surface.

Varying the composition of drug reservoir formulation, the permeability coefficient and thickness of rate controlling membrane can alter the drug release rate.

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

The intrinsic rate of drug release from this type of TDD system is defined by

$$\frac{dQ}{dt} = \left[\frac{Km/r\ Ka/m\ Da\ Dm}{Km/r\ Dm\ ha + Ka/m\ Da\ hm}\right]C_R$$

Where, C_R is drug concentration in reservoir compartment.

$K_{M/R}$ the partition coefficient for the interfacial partitioning of drug from the reservoir to the membrane.

$K_{A/M}$ the partition coefficient for the interfacial partitioning of drug from membrane to adhesive.

D_A diffusion coefficient in rate controlling membrane.

D_M diffusion coefficient in adhesive layer.

HA thickness of rate controlling membrane.

H_M thickness of adhesive layer.

Polymer matrix diffusion-controlled TDD systems:

In this system, the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix and then the medicated polymer formed is molded into medicated disks with defined surface area and thickness. This drug reservoir containing polymer disk is then mounted on occlusive baseplate in a compartment fabricated from a drug-impermeable plastic backing. Instead of coating adhesive polymer directly on the surface of medicated disk, it is applied along the circumference of the patch to form a strip of adhesive rim surrounding the medicated disk. E.g. Nitro-Dur system and NTS system for angina pectoris.

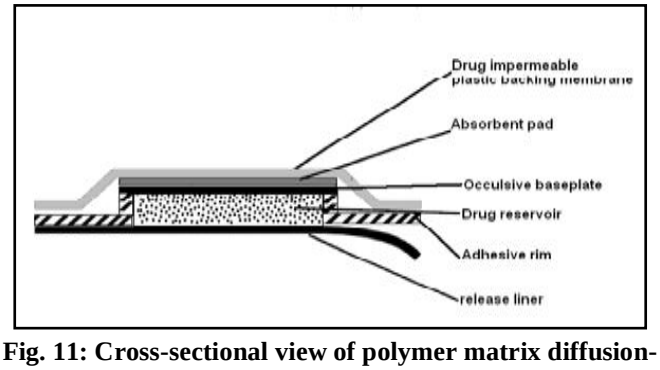

Fig. 11: Cross-sectional view of polymer matrix diffusion-controlled TDD systems.

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

$$\frac{dQ}{dt} = [LdCpDp/2t]^{1/2}$$

Where, L_D is drug loading dose initially dispersed in polymer matrix.

C_P is solubility of drug in polymer matrix.

D_P is diffusivity of drug in polymer matrix.

Only drug dissolved in polymer matrix can diffuse, C_P is practically equal to C_R.

Drug reservoir gradient-controlled TDD systems

Polymer matrix drug dispersion-type TDDS can be modified to have the drug loading level varied in an incremental manner, forming a gradient of drug reservoir along the diffusional path across the multi-laminate adhesive layers.

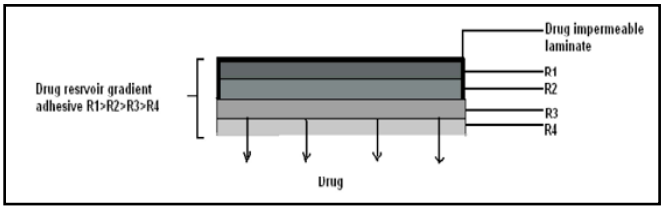

Fig. 12 Cross-sectional view of a drug reservoir gradient-controlled TDD system

The drug release from this type of drug reservoir gradient- controlled TDDS can be expressed by:

DQ/ DT = (ACpDp/2t) 1/2

Where,

A–Initial drug loading dose dispersed in the polymer matrix.

Cp and DP – are solubility and diffusivity of the drug in the polymer.

Thus, theoretically this should increase a more constant drug release profile. E.g. Deponit system containing nitroglycerine for angina pectoris.

Micro-reservoir dissolution-controlled TDD systems:

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

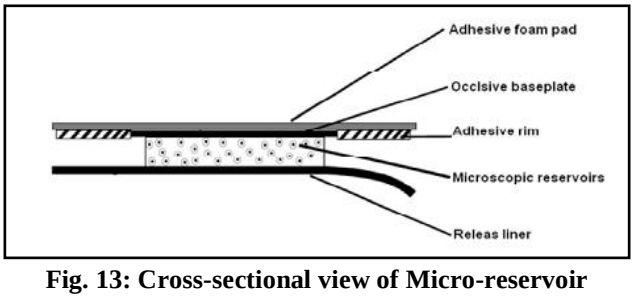

Fig. 13: Cross-sectional view of Micro-reservoir dissolution-controlled TDD systems.

This thermodynamically unstable system is quickly stabilized by immediately cross-linking the polymer chains in situ, which produces a medicated polymer disk with a constant surface area and a fixed thickness. Medicated disk is mounted at the center of an adhesive pad. E.g. Nitrodisk system for angina pectoris.

$$\frac{dQ}{dt} = \frac{DpDs\ \alpha Kp}{Dp\delta d + Ds\delta p\alpha k}[\beta S_p - D_1 S_1(1-\beta)/\delta_1\{1/K_1 + 1/K_m\}]$$

Where,

Kl, Km and KP - are partition coefficients for the interfacial partitioning of drug in the liquid compartment and the polymeric matrix.

Dl, DP and DS- drug diffusivities in the liquid compartment, polymer coating membrane and elution solution.

Sl and SP – Solubilities of the drug in the liquid compartment and polymer matrix.
δl, δP and δd – thicknesses of the liquid layer, polymer coating membrane and hydrodynamic diffusion layer.
β – Is the ratio of the drug concentration at the inner edge of the interfacial barrier over the drug solubility in the polymer layer.

11. Method of Preparing Transdermal Patches:

Method of preparation of TDDS was summarized by modifying the earlier reported methods.

The patches were prepared by solvent casting method. The polymer (for example PVP/HPMC) was taken in a beaker with a minimum quantity of the solvent. Then 2/3rd of the solvent was mixed with the other polymers (for example PVA) and was added firstly with stirring at lower rpm and later at a higher speed.

The plasticizer was added and homogeneously mixed and the drug was included with enduring agitation and the volume was made up.

The films were cast onto a suitably designed and fabricated glass mould and then dried in oven at 40^{o}C. The films were removed by using sharp blade by inserting along the edges of the film.

The dried films were wrapped in butter paper and stored in a closed container away from light and in cool place.

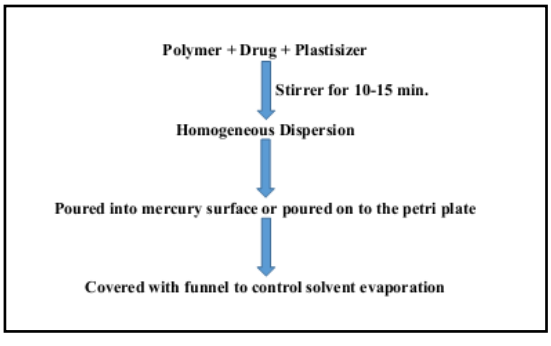

Fig. 14 Method of Preparing Transdermal Patches.

Mechanism of Action of Transdermal Patches: [23]

The function of the transdermal patch and the flow of the active drug ingredient from the patch to the circulatory system via skin transpire through different methods. For a systemically active drug to reach a target tissue, it has to take some physicochemical properties which make easy the sorption of the drug through the skin and enter the microcirculation.

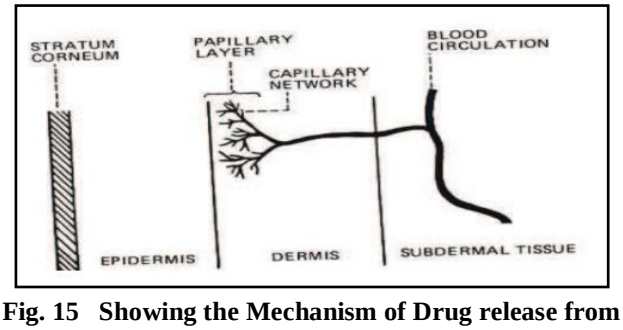

Fig. 15 Showing the Mechanism of Drug release from Transdermal Patch

Modern Techniques of Transdermal Drug Delivery System: [24-30]

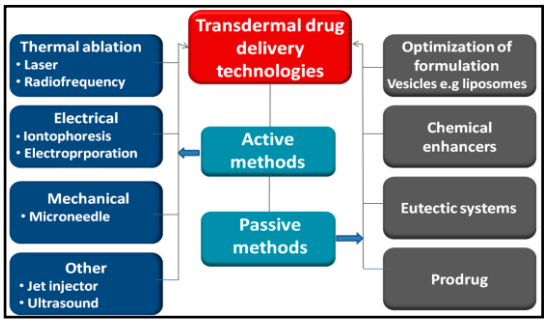

Fig. 16: Approaches for enhancing drug transport across the skin

• Iontophoresis:

It involves passing of current (few milli amperes) to skin limited to a certain area using the electrode remains in contact with the formulation which is to be administered. Pilocarpine delivery can be taken as example to induce sweat in the diagnosis of cystic fibrosis and Iontophoretic delivery of lidocaine is considered to be a nice approach for rapid onset of anesthesia.

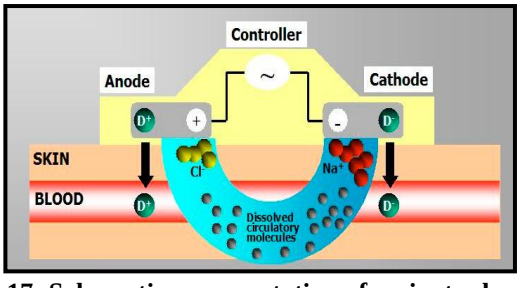

Fig. 17: Schematic representation of an iontophoresis patch with permission.

• Electroporation:

Electroporation involves the application of high - voltage pulses to induce skin perturbation. High voltages (≥100 V) and short treatment durations (milliseconds) are most frequently employed. The increase in skin permeability is suggested to be caused by the generation of transient pores during electro-poration. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e., small molecules, proteins, Peptides, oligo nucleotides).

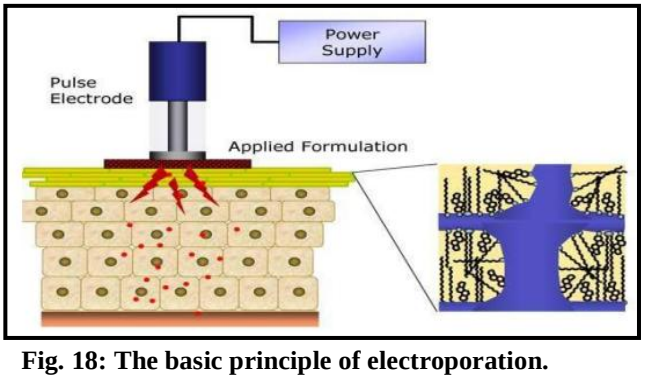

Fig. 18: The basic principle of electroporation. Short pulses of high voltage current are applied to the skin producing hydrophilic pores in the intercellular bilayers via momentary realignment of lipids.

• Magnetophoresis:

This method involves the application of a magnetic field which acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin. Skin exposure to a magnetic field might also induce structural alterations that could contribute to an increase in permeability. In vitro studies showed a magnetically induced enhancement in benzoic acid flux, which was observed to increase with the strength of the applied magnetic field. The effect of magnetic field on diffusion flux of drug substance was found to enhance with increasing applied strength.

• Ultrasound (phonophoresis, sonophoresis):

This technique, used originally in physiotherapy and sports medicine, applies a preparation topically and massages the site with an ultrasound source. The procedure was extended to transdermal drug delivery studies. The ultrasonic energy (at low frequency) disturbs the lipid packing in SC by cavitation. Shock waves of collapsing vaccum cavities increase free volume space in bimolecular leaflets and thus enhance drug penetration into the tissue.

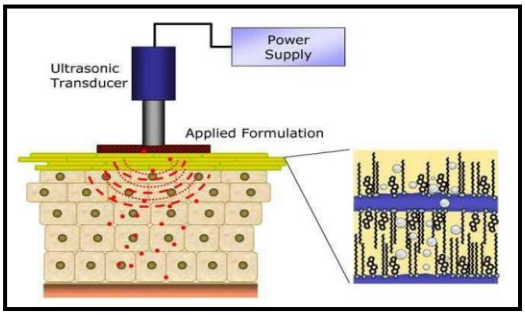

Fig. 19: The basic principle of phonophoresis. Ultrasound pulses are passed through the probe into the skin fluidizing the lipid bilayer by the formation of bubbles caused by cavitation.

• Microscissuining:

It is a process which creates micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules.

• Microporation:

Microporation involves the use of micro needles that are applied to the skin so that they pierce only the stratum corneum and increase skin permeability. Microneedles are needles that are 10 to 200 µm in height and 10 to 50 µm in width. Microneedles do not stimulate the nerves, so the patient does not experience pain or discomfort. They are usually drug coated projections of solid silicon or hollow, drug filled metal needles.

• Skin Abrasion:

In this technique, the upper layers of the skin is directly removed or disrupted, so that it easily helps in permeation of topically applied medicaments. There are also some devices that are based on techniques which are employed by dermatologists for superficial skin resurfacing (e.g. micro dermabrasion) that have use in the treatment of acne, scars, hyper pigmentation and other skin blemishes.

• Needle- Less Injection:

In this transdermal delivery system, the liquid or solid particles are fired at supersonic speeds through the outer layers of the skin using a reliable energy source for delivering the drug. The mechanism is basically, forcing compressed gas (helium) via a nozzle, such that the resultant drug particles entrained within the jet flow that travels at sufficient velocity for skin penetration.

• Microneedles:

Microneedles developed as a means to deliver drugs into the skin by invasive manner. Solid micro needles have been shown to painlessly pierce the skin to increase skin permeability to a variety of small molecules, nanoparticles sand proteins from an extended -rele ASE Patch. Microneedles have been dip coated with a variety of compounds such as small molecules, DNA, proteins, and virus particles. In a recent study, naltrex one was administered to healthy volunteers whose skin was pre - treated with micro needles. After applying the naltrex one patch, therapeutic levels of naltrex one achieved.

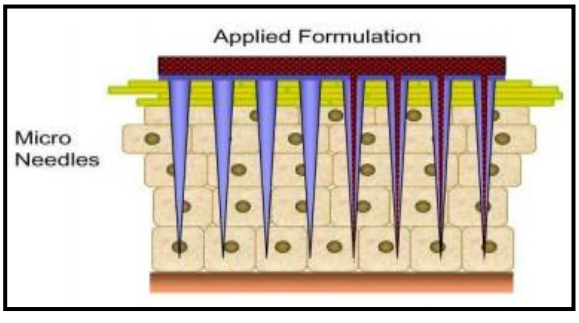

Fig. 20: Schematic representation of the mechanism of action of a micro-needle array.

• Electro -Osmosis:

To the porous membrane which is having some charge, a voltage difference is applied to it, thus a bulk fluid or volume flow takes place with no concentration gradients. This process is known as electro -osmosis.

• Laser Radiation:

This method involves direct and controlled exposure of a laser to the skin which results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs. Photomechanical waves significantly led to the stratum cornea highly permeable to drug substance through a possible permeabilisation mechanism due to development of transient channels.

• Thermophoresis:

The skin surface temperature is usually maintained at 32°C tetracaine and fentanyl from transdermal patches with attached heating devices was shown to increase as a result of the elevated temperature at the site of delivery. However, the effect of temperature on the delivery of penetrates greater than 500 Daltons has not been reported.

Evaluations of transdermal patches: [31-39]

The evaluation methods for transdermal dosage form can be classified into following types:

1) **Physicochemical evaluation**
2) ***In-vitro* evaluation**
3) ***In-vivo* evaluation**
4) **Stability studies**

1) Physicochemical evaluation

Thickness

The thickness of films was measured by digital Vernier calipers with least count 0.001 mm. The thickness uniformity was measured at five different sites and average of five readings was taken with standard deviation

Rolling Ball Tack Test

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.

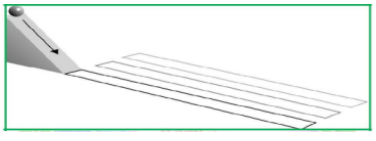

Fig. 21: Rolling ball tack test

Weight variation

The three disks of 2*2 cm^2 was cut and weighed on electronic balance for weight Variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

Percentage Elongation

The percentage elongation break is to be determined by noting the length just before the break point from the below mentioned formula.

$$\% \text{ Elongation} = \frac{L1 - L2}{L2} * 100$$

Where, L1- is the final length of each strip

L2- is the initial length of each strip.

Folding endurance

This was determined by repeatedly folding one patch at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

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.

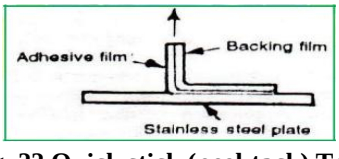

Fig. 22 Quick stick (peel-tack) Test

Tensile Strength

The tensile strength was determined by the apparatus designed as shown in fig 13. The instrument was designed such that it had horizontal wooden platform with fixed scale and attachments for two clips that holds transdermal patch under test. Out of the two clips one was fixed and other was movable. Weights were hanged to one end of pulley and the other end of pulley was attached with movable clip. The wooden platform was such fitted that it would not dislocate while the test is running. Three strips of patch were cut having 2cm length and 2cm breadth. The thickness and breadth of strips were noted at three sites and average value was taken for calculation. The rate of change of stress was kept constant with the increment of 0.5 g per 2 minutes. The elongation was observed and the total weights taken were used for calculation. The tensile strength was calculated by using following formula.

$$\text{Tensile Strength} = \frac{\text{Breaking force}}{\text{ab}} * (1 + \Delta\frac{L}{L})$$

Where, L - Length, b – Thickness,

a – Width, ΔL- Elongation at break

Shear strength properties or creep resistance

Shear strength is the measurement of the cohesive strength of an adhesive polymer i.e., device should not slip on application determined by measuring the time it takes to pull an adhesive coated tape off a stainless plate. The test performed with an apparatus which was fabricated according to PSTC-7 (pressure sensitive tape council) specification.

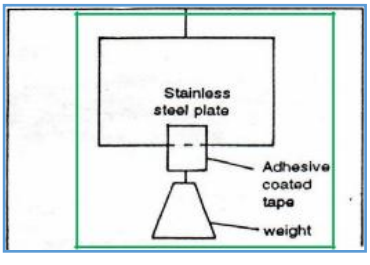

Fig. 23: Shear strength properties or creep resistance

Moisture content:

The films were weighed and kept in desiccator containing calcium chloride at 40°C in a dryer for at least 24 hours or more until it showed a constant weight. The percentage of moisture content was the difference between constant weight taken and the initial weight and as reported in terms of percentage by weight moisture content.

$$\text{Percentage moisture content} = \frac{\text{Initial wt.} - \text{Final wt.}}{\text{Final wt.}} * 100$$

Moisture uptake study

After films, of which the size is 2x2 cm^2, were put in a desiccator with silica gel for 24 hours and weighed, the films were transferred to another desiccator containing saturated solution of potassium chloride solution (relative humidity 85%) after equilibrium was attained, the films were taken out and weighed. Moisture uptake capacity was calculated according to the following equation:

$$\text{Percentage Moisture Uptake} = \frac{\text{Final wt.} - \text{Initial wt.}}{\text{Initial wt.}} * 100$$

Swelling index

The patches of 2*2 cm² was weighed and put in a Petri-dish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed. The degree of swelling (% S) was calculated using the formula

$$S\ (\%) = W_t - W_o/W_o \times 100$$

Where, S is percent swelling, Wt is the weight of patch at time t and

W_O is the weight of patch at time zero

Drug content

The film sample of 2x2cm^2 was cut and dissolved in 100 ml volumetric flask containing phosphate buffer (pH7.4), the flask was sonicated for 15 min. A blank was prepared in the same manner using drug free placebo film of same area. The solution was then filtered using a 0.45 µm filter and the drug content was analyzed at 238 nm by UV spectrophotometer.

2)*In-vitro* Evaluation:

Diffusion Cell

The design and development of the transdermal drug delivery system is greatly aided by *In-vitro* studies. The diffusion studies were done to get an idea of permeation of drug through barrier from the transdermal system. Usually, two types of diffusion cells are used as horizontal and vertical. The Franz and Keshary Chien (K-C) type of diffusion cells are of horizontal type of cells. In this work, K-C type of diffusion cell was used. Diffusion cells generally comprise two compartments, one containing the active compartment (donor compartment) and the other containing receptor solution (receptor compartment), separated by barrier i.e. rat abdominal skin. The cell consisted of sampling port and temperature maintaining jacket. The outlet and inlet was connected with latex tube so the jacket had stagnant water inside and heat was provided by hot plate. The star head magnet was used to stir the receptor solution using magnetic stirrer. The rat abdominal skin was placed on receptor compartment and both compartments held tight by clamps.

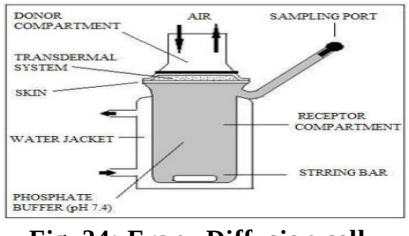

Fig. 24: Franz Diffusion cell.

Method:

The glass diffusion cell (Keshary–Chien type) was used for release studies. The cellophane membrane was mounted between donor and receptor compartment, such that the epidermal surface facing the donor compartment. The transdermal patch was fixed on between donor and receptor compartments were clamped together and placed in a water bath maintained at 37 ± 0.5°C. The volume of receptor cell was 22 ml and the effective surface area available for permeation was 4.9062 cm^2. The receptor compartment filled with pH 7.4 phosphate buffer. The hydrodynamics of the receptor fluid was maintained by stirring the fluid at 600 rpm with star head magnet. Samples 2 ml were withdrawn at specific interval of time. The same volume of phosphate buffer pH 7.4 was added to receptor compartment to maintain sink conditions and the samples were analyzed at 238 nm UV-spectro-photomertically.

3) *In vitro* drug release studies

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5°C. The paddle was 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.

4) *In vivo* Evaluation

In vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during *in vitro* studies can be fully explored during *in vivo* studies. *In vivo* evaluation of TDDS can be carried out using:

a) Animal models:

Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted lead us to a conclusion that hairless animals are preferred over hairy animals in both *In- vitro* and *In- vivo* experiments. Rhesus monkey is one of the most reliable models for *In- vivo* evaluation of transdermal drug delivery in man.

b) Human models

The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug.

c) **Biophysical Models**

Models based on steady-state mass balance equation, solution of Fick's second law of diffusion for the device, stratum corneum and viable epidermis, as well as linear kinetics have been described in the literature. It can be concluded that many techniques for in-vivo evaluation of transdermal systems have been put forward there is scope for further refinement. Some of the unresolved issues include the barrier function of the skin with age, skin metabolism, *in-vivo* functioning of penetration enhancers etc.

4. Stability studies:

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 were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.

12. Applications of Transdermal Patches:

The highest selling transdermal patch in the United States is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking.

1) Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis. Other transdermal patches for hormone delivery include the contraceptive patch (marketed as Ortho Evra or Evra).
2) Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.
3) The anti-hypertensive drug Clonidine is available in transdermal patch form.
4) Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.
5) Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD).
6) Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans).

TDDS Marketed Products:

Product	Drug	Manufacturer	Indication
Climara	Estradiol	3M Pharmaceuticals/ Berlex Labs	Postmenstrual Syndrome
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Estraderm	Estradiol	Alza/Norvatis	Postmenstrual syndrome
Habitraol	Nicotine	Novartis	Smoking cessation
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Nicotrol	Nicotine	Cygnus Inc./McNeil Consumer Products, Ltd.	Smoking cessation
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking Cessation
Ortho EvraTM	Norelgos tromin/ Ethinyl Estradiol	ORTHO-McNEIL	Postmenstrual syndrome
Alora	Estradiol	TheraTech/Proctol and Gamble	Post menstrual syndrome
Fem Patch	Estradiol	Parke-Davis	Postmenstrual syndrome

Future Prospects:

Future novel formulation approaches and technologies include liposomes, niosomes and micro emulsion. Aim of this strategy is to improve delivery of drug that has low inherent solubility in most of classical formulation excipients. 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).

The transdermal drug delivery systems (TDDS) have been designed as an alternative, safest and easy route for systemic drug delivery. The systemic drug administration though skin holds several advantages such as maintenance constant drug level in blood plasma, less number of side effects, and improvement of bio availability by circumvention of hepatic first pass metabolism and increase patient compliance with respect to drug regime used for treatment. In recent times, skin considered as a safest port for drug administration, to provide continuous drug release into systemic circulation.

13. Conclusion

Transdermal drug delivery systems represent a beneficial innovation for drug delivery, particularly in patients who cannot swallow or remember to take their medications. 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 article provides valuable information regarding the formulation and 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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