INTRODUCTION

Evolution has provided the mammalian organism with an external covering, the principal function of which is to act as a barrier, specifically to the loss of tissue water and temperature. Skin is a route for systemic drug administration also. The concentration of water inside the human body is of the order of 50M, while that in the atmosphere is clearly very much less. So, there is a strong driving force for water to be lost from the body and to prevent desiccation, an efficient barrier at the interface is therefore required. The skin provides this shield. Skin also presents a formidable resistance to the absorption either deliberate or accidental of chemicals, which contact the external surface. It stabilizes temperature and blood pressure with its circulation and evaporation systems (Barry, 1983).

Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. Pharmaceutical scientists have accepted the challenge of transdermal drug delivery over the last 25 years. The skin offers a large (1-2 m²) and very accessible surface for drug delivery. Transdermal applications, relative to other routes are quite non-invasive, requiring the simple adhesion of a “Patch” much like the application of a Band-Aid®.

Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation, oestradiol (alone or in combination with levonorgestrel or norethisterone) for hormone replacement and testosterone for hypogonadism (Benson, 2005).

The effectiveness and better patient compliance is driving a steady increase in the use of transdermal patches that deliver an array of drugs ranging from pain relievers, hormones and drugs acting on cardiovascular system. Transdermal drug delivery systems are self contained, discrete dosage forms which, when applied to the intact skin, permit absorption of drug from the tissue surface of the intact skin, through its layers into the general circulation, at controlled rates, resulting in sustained blood levels for longer period of times (Monkhouse and Hug, 1988).
Despite the small number of drugs currently delivered via this route, it is estimated that worldwide market revenues rate of 12% with current worldwide market for transdermal products are US$3B, shared between the USA at 56%, Europe at 32% and Japan at 7%. In a recent market report it was suggested that the growth rate for transdermal delivery systems will increase 12% annually as per (Front Line Strategic Consulting Inc).

In particular, the simplicity and compliance aspects of patches make it more popular especially with the paediatric and geriatric patients. Also, the patients who cannot swallow the oral solid dosage forms and no longer want a daily commitment in the administration of their medication will be more inclined to uses patches in the near future.

The oral route of administration has certain disadvantages such as destruction of drugs by hepatic first pass metabolism and enzymatic degradation within the gastrointestinal tract. Continuous intravenous administration at a programmed rate has been recognized as a superior mode of drug delivery not only to bypass hepatic first pass effect, but also to maintain a constant, prolonged and therapeutically effective drug level in the body.

The transdermal drug delivery systems are devoid of these disadvantages, in addition, their potential benefits include easy terminal drug input in case of adverse effects, permits use of drugs with a short biological half life, avoidance of absorption variability and differential metabolism associated with oral therapy.

The simply designed transdermal patch has undergone a dramatic transformation over the past decade. All transdermal systems attempt to create a balance between a number of key factors including size of patch or coverage area, concentration of the drug, duration of therapeutic drug level and use of a skin penetration enhancer.

The first transdermal systems were simply pieces of plastic dipped into a drug that was dissolved in alcohol. The plastic had an adhesive around the edges. Although revolutionary in their day, they created a significant number of skin reactions, more often than not fell off, and had a number of other limitations. These problems gave a lasting negative impression of the whole sector (Morrow, 2004).
The next generation - still in use today - uses a "drug in the adhesive" model. This is a significant improvement, as the skin irritation is diminished and in many cases eliminated. The adhesive serves two functions: It is the glue that keeps the patch attached to the skin, and it acts as the suspension that holds the drug. But it creates a major challenge: The concentration of the drug within the adhesive directly affects the "stickiness" of the adhesive. Thus, if there is a need for large quantities of drug, either the size of the patch must be increased or the patch needs to be reapplied more frequently. Basically, the patch would not stick, as it would be primarily made up of the drug.

Third generation patches have solved some of these issues by using an acrylic reservoir that holds the drug. Silicon adhesive is added to create a semisolid suspension of microscopic, concentrated drug cells.

Now, fourth generation transdermal systems involve the addition of an enhancer a mechanism to increase the permeability of the skin and in some of the technology, a mechanism to preset the time of delivery and create bolus dosing. There are a number of enhancers to drug delivery. These include iontophoresis, ultrasound, chemicals including gels, microneedles, sonophoresis, lasers, and electroporatic methods (Morrow, 2004).

It is worldwide marketed for the treatment of hypertension and heart failure and is currently being reviewed for use by the Food and Drug Administration. Nebivolol has to be well tolerated with a less adverse event profile, if better, than that of other beta-adrenergic blockers. Studies concluded that long-term therapy with nebivolol improves left ventricular function, clinical endpoints of death, exercise capacity and cardiovascular hospital admissions in patients with stable heart failure (Veverka et al., 2007).

The present research work deals with the formulation and evaluation of the matrix type transdermal drug delivery system for Nebivolol using synthetic polymers i.e. Eudragit RL100 or Eudragit RS 100 & HPMC. These copolymers offers several advantages like non-toxic, biocompatible, biodegradable, high availability and low cost, ease of chemical modification along with exhibiting suitable controlled release characteristic of the controlled drug delivery system (Sannino, et al., 2009).

In order to overcome these problems associated with Nebivolol and improve its bioavailability, reduces its dose and thereby would reduce its dose dependent side effects,
it was decided to formulate the matrix-type transdermal delivery system with Nebivolol as a model drug.

A novel beta-blocker, Nebivolol, has been approved by the US Food and Drug Administration (FDA) in January 2008 for the treatment of hypertension. The drug is a selective $\beta_1$-adrenergic blocking agent and has the added pharmacological properties, peculiar pharmacodynamic profile and an original chemical structure of producing vasodilation and reducing total peripheral resistance brought about by modulation of nitric-oxide release.

Nebivolol is a racemic mixture of two enantiomers in equal ratios. Nebivolol is endowed with peripheral vasodilating properties and with a highly selective $\beta_1$-blocking activity, and does not show an intrinsic sympathomimetic activity (Mangrella et al., 1998).

The drug delivery by transdermal route could show sustained plasma profile over long period of time. This could minimize the risk of fluctuations of drug plasma levels. Finally it is non-invasive technique, easy to terminate the action by removing the patch from the site and most importantly it improves the patient compliance.

1.1 ANATOMY PHYSIOLOGY AND FUNCTION OF THE HUMAN SKIN

Human skin is a uniquely engineered organ that permits terrestrial life by regulating heat and water loss from the body whilst preventing the ingress of noxious chemicals or microorganisms. It is the large and easily accessible organ apparently offers ideal and multiple sites to administer therapeutic agents for both local and systemic actions, human skin is a highly efficient self-repairing barrier designed to keep ‘the insides in and the outside out’. It is a largest organ of the human body, providing around 10% of the body mass of an average person and it covers an average area of 1.7 m$^2$. Skin membranes can be examined at different levels of complexity. In some mathematical treatments of transdermal drug delivery, the membrane can be regarded as a simple physical barrier; more complexity can be introduced by viewing skin as various barriers in series. The barriers can be introduced in parallel by considering drug transport through pores in the tissue. Degrees of complexity also exist when examining basic structures and functions of the membrane. In some extremely the transdermal drug delivery is limited by
metabolic activity within the membrane. Alternatively, immunological responses may prevent the clinical use of a formulation that has proven to be optimal during \textit{in vitro} studies.

1.2 HEALTHY SKIN STRUCTURE AND FUNCTION

Human skin is a highly complex organ though in various transdermal drug delivery studies it is often regarded somewhat simplistically as merely a physical barrier. \textit{In vivo}, skin is in a process of continual regeneration, it has immunological and histological responses to assault (as would be the cases if an exogenous chemical, such as a drug, were applied to the surface) and is metabolically active. Due to experimental and ethical difficulties, most transdermal drug delivery studies tend to utilize skin \textit{ex vivo (in vitro)}, which inherently reduces some of the above complexity—regeneration stops, immune responses cease and metabolic activity is usually lost in these studies. However, it should always be borne in mind that data obtained from excised skin may not translate directly to the \textit{in vivo} situation. Human skin comprises of three distinct but mutually dependent tissues (Fig. 1).

A) The stratified, vascular, cellular epidermis, (Keleb et al., 2010; Tortara et al., 2000; Schofield et al., 2002; Vyas et al., 2002)

B) Underlying dermis of connective tissues and

C) Hypodermis.
1.2.1 Epidermis

The multilayered of epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.06 mm on the eyelids sole and 0.8 mm on palms.

1.2.1.1 Horney layer (Stratum corneum)

This is the outermost layer of skin also called as horney layer. It is approximately 10μm 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. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration of drug. The structure of horney layer may be modeled as a wall-like structure.
1.2.1.2 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. As the cells produced by the basal layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum corneum.

1.2.2 Dermis

Dermis is 3 to 5mm thick layer of skin and is composed of a matrix type connective tissue, which contains blood vessels, lymph vessels and nerves. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The cutaneous blood supply has essential function in regulation of body temperature. 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. It also provides nutrients and oxygen to the skin while removing toxins and waste products.

1.2.3 Hypodermis

The hypodermis or subcutaneous fat tissue supports the epidermis and dermis layer. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanical protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, 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.

1.2.4 Epidermal enzyme systems

The cellular component of the epidermis layer, the tissue contains various drug-metabolizing enzymes. Histo-chemical and immune histo-chemical methodologies
suggest that the majority of these are localized in the epidermis, sebaceous glands and hair follicles. Although present at relatively small quantities in comparison to the liver, they do allow metabolic activity that can effectively reduce the bioavailability of topically applied medicaments; a common misconception is that the skin is an inert tissue. Indeed, phase 1 (e.g., oxidation, reduction, hydrolysis) and phase 2 (e.g., methylation, glucuronidation) reactions can occur within the skin, though these tend to be at <10% of the specific activities found in the liver (Hotchkiss, 1998). However, esterases tend to have relatively high activities within skin and considering that there is a large skin surface area, the metabolism of some drugs can be significant. For example, topically applied benzoyl peroxide is completely hydrolyzed to benzoic acid by human skin (Nacht et al., 1981). Such metabolic activity can also be of value; many prodrugs, notably the steroid esters such as betamethasone-17-valerate, are designed to have improved delivery characteristics (e.g., increased lipophilicity) and exploit esterase activity to liberate the free drug within the skin. Microorganisms present on the skin surface, such as Staphylococcus epidermidis, may also metabolize topically applied drugs.

1.3 PROPERTIES THAT INFLUENCE TRANSDERMAL DRUG DELIVERY

The effective transdermal drug delivery can be formulated by considering three factors as drug, skin and the vehicles. So the factors affecting can be divided in two classes as biological factors and physicochemical factors (Zhou and Wu, 1997; Sharma et al., 2011).

1.3.1 Biological factors

i) Skin condition: Acids and alkalis, many solvents like chloroform, methanol damage the skin cells and promotes penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above mentioned conditions affect penetration.

ii) Skin age: The young skin is more permeable than older. Children’s are more sensitive for skin absorption of toxins. Thus, skin age is one of the factor affecting penetration of drug in TDDS.

iii) Blood supply: Changes in peripheral circulation can affect transdermal absorption.
iv) **Regional skin site**: Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration.

v) **Skin metabolism**: Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.

vi) **Species differences**: The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration.

1.3.2 **Physicochemical factors**

i) **Skin hydration**: In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So use of humectant is done in transdermal delivery.

ii) **Temperature and pH**: The permeation of drug increase ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration.

iii) **Diffusion coefficient**: Penetration of drug depends on diffusion coefficient of drug. At a constant temperature the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.

iv) **Drug concentration**: The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.

v) **Partition coefficient**: For molecules with intermediate partition coefficient (log K 1 to 3) and for highly lipophilic molecules (log K > 3), the intercellular route will be almost the pathway used to traverse the stratum corneum. However, for these molecules a further consideration is the ability to partition out of the stratum corneum into the aqueous viable
epidermal tissues. For more hydrophilic molecules \((\log K < 1)\), the transcellular route probably predominates.

vi) **Molecular size and shape:** Firstly drug absorption is inversely related to molecular size, small molecules penetrate faster than large ones. A second major factor in calculating the flux of a material through human skin is the size of the molecule. However, for simplicity, the molecular weight is generally taken as an approximation of molecular size. It has been suggested that an inverse relationship existed between transdermal flux and molecular weight of the molecule. However, most conventional therapeutic agents that are selected as candidates for transdermal delivery tend to lie within narrow range of molecular weight (100-500 Dalton).

vii) **Other factors:** Beyond the factors mentioned above, there are other molecular properties that can affect drug delivery through the skin. Drug binding is a factor that should be born in mind when selecting appropriate candidates. Interactions between drug substances and the tissue can vary from hydrogen bonding to weak Van der Waals forces, and the effect of drug binding (if any) on flux across the tissue will vary depending on the permeant.

### 1.3.3 Pathological disorders

There are numerous dermatological textbooks that offer detailed descriptions of the clinical symptoms and pathology of skin disorders. Clearly, for many skin disorders where the barrier function is compromised, as treatment progresses the condition will improve; that is, the barrier function of the tissue may be restored to that approaching uninvolved tissue and consequently, as the disorder improves, drug delivery decreases.

#### 1.3.3.1 Eruptions

Numerous disorders result in an eruption of the skin surface. In such cases the barrier properties of the *Stratum corneum* are compromised, allowing easier passage of drugs (and potentially toxic materials) into and through the skin. Likewise, the erupted skin surface will allow increased water loss from the body. Plaques in psoriatic conditions arise from accelerated differentiation of keratinocytes through the epidermis.
and from increased mitosis of keratinocytes, not only from within the basal layer but also in the two or three cell layers above the basal layer. Numerous therapies exist, including those that inhibit mitotic activity [e.g., psoralen-UVA (PUVA) treatment]. Indeed, for topical therapy the loss of skin barrier integrity has been shown to be valuable for targeting drugs to the required site of action whilst minimizing side effects (Anigbogu et al., 1996). Lichenoid eruptions are characterized by intensely itchy, flat-topped papules. In the most common of these conditions, lichen planus, the granular epidermal layer is thickened and lymphocytes are found in the dermis near the basement membrane, suggesting that the condition is associated with an autoimmune disease. Eczema, from the Greek ‘to boil over’, is a further non-infectious eruptive condition, in which blistering occurs. Atopic dermatitis is a chronic inflammation of the epidermis usually with a strong genetic predisposition from parents who may have, for example, asthma or allergic rhinitis. Various studies have clearly demonstrated that the stratum corneum barrier is highly compromised for patients with atopic dermatitis, with transepidermal water loss from the body increasing by up to 10-fold (Ogawa and Yoshiike, 1992; Aalto-Korte and Turpeinen, 1993). Contact dermatitis can result from a direct irritant action of a substance on the skin (irritant contact dermatitis) or further exposure, following previous sensitization of the skin, from a contact allergen (allergic contact dermatitis). Irritant dermatitis is the more common of the two manifestations and can be caused by many chemicals, solvents and detergents. Irritant dermatitis tends to have a rapid onset of action (4–12 h after exposure) and is seen at the site exposed to the irritant. Sodium lauryl sulfate was used to induce irritant dermatitis before in vivo percutaneous absorption of several drugs was assessed (Wilhelm et al., 1991).

1.3.3.2 Infections

Intact skin is a highly effective barrier against the ingress of microorganisms. However, the tissue also carries microbial flora, including bacteria and yeasts and if breached, then infection can result. Commonly found skin bacteria include staphylococcal species (e.g., Staphylococcus epidermidis), micrococci, corynebacteria and propionibacteria. These organisms tend to aggregate around hair follicles where they can be numerous. For example, micrococci may number around 60 per cm² on the forearm, but up to 500,000 per cm² in the axillae. With such potentially high numbers of
organisms, it is also conceivable that some topically applied drugs may be metabolized prior to penetrating the tissue. Many diseases of the skin are caused by staphylococcal (*Staphylococcus aureus*) and streptococcal (e.g., *Streptococcus pyogenes*) organisms. Most seriously, *Streptococcus pyogenes* is the causative organism of necrotising fasciitis, an acute condition usually resulting from a minor trauma. An ill-defined erythema will rapidly become necrotic and can be fatal unless rapid surgical debridement of the tissue and systemic antibiotics are employed. Other bacterial infections, less common than those caused by the Gram-positive cocci, include infections due to mycobacteria; tuberculosis is caused by *Mycobacterium tuberculosis*, which generates the condition lupus vulgaris, characterized by red/brown plaques often on the face and neck. Warts (verrucae) are common benign cutaneous tumours caused by the human papillomavirus. They are usually self-limiting, though are transmitted by direct contact. Generally, the epidermis becomes thickened and is hyperkeratotic causing the eruption and the keratinocytes of the stratum granulosum are vacuolated because of the viral infection. Many treatments for hand warts are topically applied, though cryotherapy is usually indicated for most genital warts. Targeting of, for example, salicylic acid to the viral particles within the wart has been demonstrated from topical applications (Lawson et al., 1998). Herpes simplex (cold sores) infections are also treated topically and again are very common self-limiting vesicular eruptions. *Herpes zoster* (shingles) is similarly self-limiting, though secondary bacterial infections can be problematic. Fungal skin infections are also common and range in severity. Dermatophyte infections target the keratinised tissues of the body. The damage caused to the skin barrier integrity will vary with severity of the infection. In cases such as necrotising fasciitis it is obvious that the barrier is seriously impaired.

1.3.3.3 Ichthyosis

Ichthyoses are defined as disorders of keratinisation and epidermal differentiation. They are usually genetically determined and are characterized by excessively dry and scaly skin. Considerable thickening of the stratum granulosum with an increase in stratum corneum thickness is seen with ichthyotic conditions. However, even with a thickened stratum corneum the barrier integrity is compromised in ichthyotic patients (Lavrijsen et al., 1993).
1.3.3.4 Tumors

Skin tumors are common and numbers of cases are rising rapidly in Western countries. The majority of skin tumors are benign and those from viral warts have been described above. Benign tumors can result from a proliferation of basal layer keratinocytes or melanocytes. Some benign tumors (such as actinic keratoses) manifest as scaly hyperpigmented crusting lesions, are premalignant and usually result from an outdoor occupation or from considerable recreational sun exposure. Malignant tumours can derive from keratinocytes (such as squamous cell carcinoma), from melanocytes (malignant melanoma), or from other basal cells in the epidermis (basal cell carcinoma). Most malignant tumours are excised and may be followed by radiotherapy or chemotherapy. However, some tumours may be controlled rather than cured (such as slowly evolving T-cell lymphomas), in which case topical preparations including steroids may help to improve symptoms. Again, the stratum corneum around an eruptive tumor will be compromised.

1.4 TRANSDERMAL DRUG DELIVERY SYSTEMS

Transderm-Scop®, developed in 1980, used the drug scopolamine for the treatment of motion sickness. Although thousands of drugs could be utilized in such delivery systems, only eight drugs and 25-30 transdermal drug delivery systems (TDDS) have been developed to date. Current drugs utilized in TDDS include nicotine, nitroglycerin and various hormones such as estradiol and testosterone.

The transdermal drug delivery system can be defined as self contained discrete dosage forms which when applied to the intact skin deliver the drugs through the skin at a controlled rate to the systemic circulation (Monkhouse and Hug, 1988).
Transdermal drug delivery systems

Passive transdermal systems
Passive transdermal systems allow the drug to diffuse through the skin into the bloodstream using a simple concentration gradient as a driving force.

Active transdermal systems
Delivery systems in this category require a physical force to facilitate the movement of drug molecules across the skin.

Matrix systems
Reservoir systems

Ionophoresis
Electroporation
Sonoporation

Figure: 2. Different type of transdermal drug delivery systems

TDDS are designed to provide controlled continuous delivery of drugs directly through the skin into systemic circulation, maintaining consistent efficacy while minimizing side effects (Davila et al., 2001).

Transdermal drug administration generally refers to topical application of agents to healthy intact skin either for localized treatment of tissues, underlying the skin or for systemic therapy. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously, minimize the retention and metabolism of the drug in the skin (Misra et al., 1990).

1.4.1 Advantages (Wilkosz, 2003; Allen et al., 2002)

- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity and drug interactions with food, drink and other orally administered drugs.
- They can substitute for oral administration of medication when that route is unsuitable, as in case of vomiting and diarrhea.
They avoid the first-pass metabolism and avoid drug deactivation by liver enzymes.

They are non-invasive so avoiding the inconvenience of parenteral therapy.

They provide extended therapy with a single application, improving compliance over other dosage forms, requiring more frequent dose administration.

Drug therapy may be terminated rapidly by removal of Transdermal drug delivery systems from the surface of the skin.

They are easily and rapidly identified in emergencies (e.g. unresponsive, unconscious or comatose patient) because of their physical presence, features and identifying markings.

They can be used for drugs with narrow therapeutic window.

1.4.2 Disadvantages of TDDS (Kim et al., 2000; Panchangula et al., 2001; Manvi et al., 2003)

The drug should have some desirable physico-chemical properties for permeation through stratum corneum and if the dose required for therapeutic values is more than 20mg/day the transdermal delivery will be difficult to formulate, if not impossible.

Skin irritation or contact dermatitis due to drug, excipients and enhancers. Clinical need is another area that has to be examined carefully before developing a transdermal product.

The natural limits of drug entry imposed by the skin’s permeability indicate that relatively potent drugs are suitable only for transdermal delivery.

Bacterial and enzymatic drug metabolism under the patch.

Under various environmental conditions, adhesions of the system to different skin types, sometimes result in technical difficulties.

The barrier function of the skin changes from one site to another of the same person from person to person and with age.

1.5 BASIC COMPONENTS OF TDDS

- Polymer matrix / Drug reservoir
Drug
Permeation enhancers
Pressure sensitive adhesive (PSA)
Backing laminates
Release liner
Other excipients like plasticizers and solvents

**Polymer matrix / Drug reservoir**

Polymers are the backbone of a transdermal drug delivery system. Systems for transdermal delivery are fabricated as multilayered polymeric laminates in which a drug reservoir or a drug–polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and/or rate-controlling membrane.

Polymer selection and design must be considered when striving to meet the diverse criteria for the fabrication of effective transdermal delivery systems. The main challenge is in the design of a polymer matrix, followed by optimization of the drug loaded matrix not only in terms of release properties, but also with respect to its adhesion–cohesion balance, physicochemical properties, and compatibility and stability with other components of the system as well as with skin.

The polymers utilized for TDDS can be classified as

- **Natural Polymers**: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan *etc*.
- **Synthetic Elastomers**: e.g. polybutadiene, hydrid rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber *etc*
- **Synthetic Polymers**: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate *etc*.

The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose are used as matrix formers for
TDDS. Other polymers like EVA, silicon rubber and polyurethane are used as rate controlling membrane.

✓ **Drug**

The most important criteria for TDDS is that the drug possesses the right physicochemical and pharmacokinetic properties. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non-compliance due to frequent dosing. For example, drugs like rivastigmine for alzheimer’s and Parkinson dementia, rotigotine for parkinson, methylphenidate for attention deficit hyperactive disorder and selegiline for depression are recently approved as TDDS.

**Biopharmaceutical parameters in drug selection for transdermal patch**  
(Chandrashekhar et al., 2008)

- Dose should be low i.e <20mg/day.
- Half life should be 10 h or less.
- Molecular weight should be <500 Dalton.
- Partition coeffecient should be Log P(octanol-water) between 1.0 and 4.
- Skin permeability coefficient should be <0.5 X 10^-3 cm/h.
- Drug should be non irritating and non sensitizing to the skin.
- Oral bioavailability should be low.
- Therapeutic index should be low.

✓ **Permeation enhancers**

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 watersoluble
drugs. Pharmaceutical scientists have made great efforts in transdermal permeation studies using various enhancers for several drug moieties (Parivesh et al., 2010).

**Kinetics of Transdermal Permeation**

Skin permeation kinetics is vital to the development of TDDS. Simple diffusion laws can be used to describe the percutaneous absorption process. In TDDS, it is assumed that steady-state conditions reached and thus it follows Fick’s first law of diffusion (Mass et al., 2002), mathematically expressed as:

\[ J = K D \frac{(C_0 - C_i)}{h} \]

\( J \) = flux per unit area, \( K \) = Partition coefficient of permeant and \( D \) is its diffusion coefficient in the stratum corneum of path length \( h \), \( C_0 \) and \( C_i \) are concentrations of permeant on skin and in the body respectively, generally \( C_0 \) is much greater than \( C_i \), this simplifies the above equation to:

\[ J = K D C_0 / h \]

**Ideal characteristics of penetration enhancers** (William & Barry, 2004; Pathan & Setty, 2009)

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

✓ **Pressure sensitive adhesive**

A PSA maintains an intimate contact between patch and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy, exert a strong holding force. For eg polyacrylates, polyisobutylene
and silicon based adhesives. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. PSA should be physicochemically and biologically compatible and should not alter drug release. The PSA can be positioned on the face of the device (as in resorvoir system) or in the back of the device and extending peripherally as in case of matrix system (Saroha et al., 2011)

 ✓ **Backing laminate**

   The primary function of the backing laminate is to provide support. Backing layer should be chemical resistant and excipient compatible because the prolonged contact between the backing layer and the excipients may cause the additives to leach out or may lead to diffusion of excipients, drug or penetration enhancer through the layer. They should a low moisture vapor transmission rate. They must have optimal elasticity, flexibility, and tensile strength. Examples of some backing materials are an aluminium vapor coated layer, a plastic film (polyethylene, polyvinyl chloride, polyester) and a heat seal layer (Saroha et al., 2011).

 ✓ **Release liner**

   During storage release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. The release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metallized laminate.

 ✓ **Other excipients**

   Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylphthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.
1.5 FUNDAMENTALS OF SKIN PERMEATION

Until the last century the skin was supposed to be impermeable with exception to gases. However, in the current century the study indicated the permeability to lipid soluble drugs. Also it was recognized that various layers of skin are not equally permeable i.e. epidermis is less permeable than dermis. After a large controversy, all doubts about stratum corneum permeability were removed and using isotopic tracers, it was suggested that stratum corneum greatly hamper permeation (Chein, 2005).

1.5.1 Stratum corneum as skin permeation barrier:- The average human skin contains 40-70 hair follicles and 200-250 sweat ducts per square centimeter. Especially water-soluble substances pass faster through these ducts, still these ducts don’t contribute much for skin permeation. Therefore most neutral molecules pass through stratum corneum by passive diffusion. Regional variation in water permeability of stratum corneum.

Series of steps in sequence:
1. Sorption of a penetrant molecule on surface layer of stratum corneum.
2. Diffusion through it and viable epidermis and finally reaches to dermis and then.
3. The molecule is taken up into the microcirculation for systemic distribution.

Intracellular regions in stratum corneum are filled with lipid rich amorphous material. In dry stratum corneum intracellular volume may be 1% to 5% in fully hydrated stratum corneum.

1.5.2 Skin permeation of polar nonelectrolytes

Introduction of polar groups, such as hydroxy groups, has been reported to reduce the skin permeability of steroids. The magnitude of the reduction showed a first order dependence on the number of OH groups added to the progesterone skeleton. The relationship can be expressed as

\[
\log (P_{s})_{\text{OH}} = \log (P_{s}) - (\pi)_{\text{OH}} (n)_{\text{OH}}
\]

Where, \((P_{s})_{p}\) and \((P_{s})_{\text{OH}}\) are the permeability coefficients for progesterone and its hydroxyl derivatives respectively; \((\pi)_{\text{OH}}\) is the incremental constant for the hydroxyl
group; and is the number of OH groups. The addition of hydroxyl groups was also found to modify the pharmacokinetics profile of steroids following topical administration. The addition of an OH group to the steroidal skeleton of progesterone slowed the rate of elimination and the introduction of two or more OH groups reduced both rates of absorption and elimination.

1.5.3 Skin permeation of ionogenic compounds

For ionogenic compounds, the process of skin permeation is likely to be complicated by the simultaneous presence of both ionized and non-ionized species in the solution, each of which permeates the skin at different rates.

1.6 PERMEATION PATHWAYS

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 (Barry, 2002; Bodae & De Hnn 1994).

Figure 3. A- multilayer skin model showing sequence of Transdermal permeation of drug for systemic delivery, B-Intracellular verses transcellular diffusion
1.6.1 **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 to be of minor importance because of its relatively small area, approximately 0.1 % of the total skin area.

![Simplified representation of skin showing routes of penetration](image)

**Figure 4. Simplified representation of skin showing routes of penetration:** 1. through the sweat ducts; 2. directly across the stratum corneum; 3. via the hair follicles.

1.6.1.1 **Epidermal route**

For drugs, which mainly cross-intact horny layer, two potential micro routes of entry exists, the transcellular (intracellular) and intercellular pathways.
I. **Transcellular:** Transcellular pathway means transport of molecules across epithelial cellular membrane. These include passive transport of small molecules, active transport of ionic and polar compounds and endocytosis and transcytosis of macromolecules.

II. **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 drugs.

### 1.7 **PENETRATION ENHANCEMENT**

The perfect barrier properties of the epidermis restricts the transport through the skin to molecules with certain properties such as low molecular weight (< 500 Dalton), moderate lipophilicity (octanol–water partition coefficient between 1.0 and 4) and modest...
melting point (< 200 °C) correlating with good solubility. Even when an active substance exhibits such properties, it is usually necessary to find additional means to increase its transport across the skin.

(a) Supersaturation

Supersaturation is a means to increase skin penetration without alteration of Stratum corneum structure (Pellet et al., 2003). The mechanism of enhancement is based simply on the increased thermodynamic activity of the drug. This increases the concentration gradient \((C_O - C_i)\) in the Fick’s law and thus forces the active principle out of the formulation and into and across the stratum corneum. Several methods can be used to produce supersaturated systems:

- Heating and subsequent cooling
- Removal of a solvent
- Reaction of two or more solutes to produce a compound, which is very soluble
- Addition of substance to a solution that reduces the solubility of the solute.

However, supersaturated systems are thermodynamically unstable and inherently tend to recrystallize. Therefore special efforts are necessary to transiently stabilize the supersaturated system for an appropriate period of time, e.g., addition of polymers as anti-nucleant in order to delay re-crystallization.

(b) Water as penetration enhancer

Hydration of the Stratum corneum is one of the primary measures to increase the penetration of most active compounds. Water opens up the compact structure of the horny layer. The water content of the horny layer can be increased either by delivering water from the vehicle to the skin or by preventing water loss from the skin when partially occlusive formulations are applied to the skin.

(c) Chemical enhancers

Several excipients are able to promote the transport of an active substance across the skin barrier by a variety of mechanisms. The most important are (Barry, 2001).

- Extraction of lipids from the Stratum corneum
Introduction

- Alteration of the vehicle/skin partitioning coefficient
- Disruption of the lipid bilayer structure
- Displacement of bound water
- Loosening of horny cells
- Delamination of Stratum corneum

Chemical enhancers can be categorized into different groups (Fig. 6). Solvents like alcohols, alkylmethyl sulfoxides and polyols mainly increase solubility and improve partitioning coefficient. Moreover, some solvents, e.g., Dimethylsulphoxide (DMSO), ethanol, may extract lipids, making the Stratum corneum more permeable. Oleic acid, Azone® (epsilon-Laurocapram) and isopropyl myristate are typical examples of chemical enhancers which intercalate into the structured lipids of the horny layer where they disrupt the packing. This effect makes the regular structure more fluid and thus increases the diffusion coefficient of the permeant. Ionic surfactants, decylmethyl sulfoxide, DMSO, urea interact with the keratin structure in the corneocytes. This opens up the tight protein structure and leads to an increased diffusion coefficient D mainly for those substances, which use the transcellular route.

![Chemical structures of enhancers](image)

**Figure 6. The chemical structure of typical chemical penetration enhancers**

An unfortunate feature of many potent chemical enhancers is that they irritate due to their ability to interact effectively with the corneocytes and the intercellular lipid structure.
(d) Physical enhancement techniques

Hydration of the horny layer and addition of chemical enhancers that temporarily alter the barrier properties can enhance the flux of active substances. However, all these principles have clear limitations concerning the delivery of sufficiently high amounts of ionic molecules, large molecular weight actives and substances with low potency. These limitations of chemical enhancement can be overcome to some extent by physical enhancement technologies (Cross and Roberts, 2004).

(e) Phonophoresis

Phonophoresis (or sonophoresis) uses ultrasound energy in order to enhance the skin penetration of active substances (Cross and Roberts, 2004). When skin is exposed to ultrasound, the waves propagate to a certain level and cause several effects that assist skin penetration. One of these effects is the formation and subsequent collapse of gas bubbles in a liquid called cavitation. The force of cavitation causes the formation of holes in the corneocytes, enlarging of intercellular spaces and perturbation of Stratum corneum lipids. Another effect is heating which is mainly due to the energy loss of the propagating ultrasound wave due to scattering and absorption effects. The resulting temperature elevation of the skin is typically in the range of several degrees centigrade. This temperature rise will increase the fluidity of the Stratum corneum lipids as well directly increase the diffusivity of molecules through the skin barrier. These main effects can be assisted by acoustic micro streaming caused by the acoustic shear stress, which is due to unequal distribution of pressure forces. In addition, ultrasound can push particles through by pressure increase in the skin, although only slightly.
(f) Iontophoresis

The basic principle of iontophoresis is that a small electric current is applied to the skin. This provides the driving force to primarily enable penetration of charged molecules into the skin. A drug reservoir is placed on the skin under the active electrode with the same charge as the penetrant. An indifferent counter electrode is positioned elsewhere on the body. The active electrode effectively repels the active substance and forces it into the skin. This simple electro-repulsion is known as the main mechanism responsible for penetration enhancement by iontophoresis. The number of charged molecules which are moved across the barrier correlates directly to the applied current and thus can be controlled by the current density. Other factors include the possibility to increase the permeability of the skin barrier in the presence of a flow of electric current and electro-osmosis. Contrary to electro-repulsion, electro-osmosis can be used to transport uncharged and larger molecules. Electro-osmosis results when an electric field is applied to a charged membrane such as the skin and causes a solvent flow across this membrane. This stream of solvent carries along with it dissolved molecules. It enhances the penetration of neutral and especially polar substances.
(g) Electroporation

Electroporation is also based on the application of a voltage to the skin (Preat and Vanbever, 2003). In contrast to iontophoresis where a low voltage is applied, electroporation requires a large voltage treatment for a short period of 10 ms to 100 ms. Electroporation produces transient hydrophilic pores (aqueous pathways) across the skin barrier (Fig. 9). These pores allow the passage of macromolecules via a combination of diffusion, electro-phoresis and electro-osmosis.
In the last years, several attempts have been made to enhance the transport of substances across the skin barrier using minimally invasive techniques (Down and Harvey, 2003). The proper function of an appropriate system requires that the thickness of the Stratum corneum (10 to 20 µm) has to be breached. More recent developments focus on the concept of micro-needles. Micro-needles are needles that are 10 to 200 µm in height and 10 to 50 µm in width (Fig. 10). They are solid or hollow and are connected to a reservoir, which contains the active principle.

![Figure 10. The basic design of micro-needle delivery devices. Needles of approximately with or without centre hollow channels are placed onto the skin surface so that they penetrate the stratum corneum and epidermis without reaching the nerve endings present in the upper dermis.](image)

Micro-needle arrays are applied to the skin surface so that they pierce the upper epidermis far enough to increase skin permeability and allow drug delivery, but too short to cause any pain to the receptors in the dermis. Therefore there is no limitation concerning polarity and molecular weight of the delivered molecules. The fabrication of such tiny structures became possible with the advent of micro machining technology, which is an essential technology for the microelectronic industry.

It is not difficult to imagine that micro needle systems can be easily combined with microelectronic elements, which can fully control the delivery rate. Furthermore, this type of system could be linked to a micro sensor system, which measures the actual concentration of an active molecule, which then triggers the release. It can be envisioned that such a ‘pharmacy on a chip’ may be the future drug delivery.
Formulation approaches

Penetration enhancement with special formulation approaches is mainly based on the usage of colloidal carriers. Submicron sized particles are intended to transport entrapped active molecules into the skin. Such carriers include liposomes, nano-emulsions and solid-lipid nanoparticles (Fig. 11). Most reports cite a localizing effect whereby the carriers accumulate in stratum corneum or other upper skin layers. Generally, these colloidal carriers are not expected to penetrate into viable skin. However, the effectiveness of these carriers is still under debate.

![Figure 11. The structure of nano-dispersed vehicle systems](image)

More recently a new type of liposomes called transferosomes has been introduced. Transferosomes consist of phospholipids, cholesterol and additional surfactant molecules such as sodium cholate. The inventors claim that transferosomes are ultradeformable and squeeze through pores less than one-tenth of their diameter. Thus 200 to 300 nm-sized transfereosomes are claimed to penetrate intact skin. Penetration of these colloidal particles works best under *in vivo* conditions and requires a hydration.

Another formulation approach aiming to enhance skin penetration is the preparation of micro-emulsions. Such systems consist of water, oil and amphiphilic compounds (surfactant and co-surfactant), which yield a transparent, single optically isotropic and thermodynamically stable liquid. Micro-emulsions can be either oil continuous, water continuous, or bi-continuous. The main difference between macro-
emulsions and micro-emulsions lies in the size of the particles of the dispersed phase: these are at least an order of magnitude smaller in the case of micro-emulsions (10 - 200 nm) than those of conventional emulsions (1-20 µm). Typical properties of micro-emulsions include optical transparency, thermodynamic stability, and solubility of both hydrophobic and hydrophilic components. Penetration enhancement from micro-emulsions is mainly due to an increase in drug concentration, which provides a large concentration gradient from the vehicle to the skin. Furthermore it has been suggested that the surfactants and the oil from the micro-emulsion interact with the rigid lipid bilayer structure and acts as a chemical enhancer (Schmalfuss et al., 1997).

1.7 Prodrug Approaches

The prodrug approach has been investigated to enhance dermal and transdermal delivery of drugs with unfavourable partition coefficients (Sloan & Wasdo, 2003). The prodrug design strategy generally involves addition of a promoiety to increase partition coefficient and hence solubility and transport of the parent drug in the stratum corneum. The intrinsic poor permeability of the very polar 6-mercaptopurine was increased up to 240 times using S6- acyloxymethyl and that of 5-fluorouracil, a polar drug with reasonable skin permeability was increased up to 25 times by forming N-acyl derivatives (Beall & Sloan, 2002). The prodrug approach has also been investigated for increasing skin permeability of non-steroidal anti-inflammatory drugs (Davaran et al., 2003; Doh et al., 2003), b-blockers and other drugs.

Charged drug molecules do not readily partition into or permeate through human skin. Formation of lipophilic ionpairs has been investigated to increase stratum corneum penetration of charged species. This strategy involves adding an oppositely charged species to the charged drug, forming an ion-pair in which the charges are neutralised so that the complex can partition into and permeate through the stratum corneum. The ion-pair then dissociates in the aqueous viable epidermis releasing the parent charged drug which can diffuse within the epidermal and dermal tissues (Megwa et al., 2000a; Megwa et al., 2000b; Valenta et al., 2000). In general permeability increases of only two to three-fold have been obtained although (Sarveiya et al., 2004). Recently reported a 16-fold increase in the steady-state flux of ibuprofen ionpairs across a lipophilic membrane.