INTRODUCTION

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MAN HAS had been trying to find drugs since long, which would cure ills without producing harmful, undesirable or unpleasant effects. Ehrlich's dream of the magic bullet having "a minimum organotropic action" has been the guiding star. Discovering new drugs is extremely costly and the results are erratic. The attention of pharmaceutical scientists is being focused on the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and or targeting the delivery of drug to infected organ or tissues. This advancement have led, to the development of several novel drug delivery systems that would revolutionize the method of medication and provide a number of therapeutic benefits.

To achieve better patient compliance and to control the time course of drugs in the body, new products called controlled release, sustained release, prolonged action, time release and repeat action etc are developed. To appreciate their value, one should know the limitations of conventional dosage forms like tablets, capsules, when these are administered, the drug blood level vs time profile is of a saw – tooth type resulting in peak and valley type oscillating drug kinetics which is undesirable. This is more dangerous for drugs whose toxic and therapeutic drug levels are close or in other words the drugs have a narrow therapeutic index. Hence, it is required to deliver certain drugs at a constant or zero order rate by developing controlled drug delivery system, which deliver drug in precise quantities over a period of time (Breimer, 1984).

Discovering a new drug molecule is very costly; therefore the therapeutic efficacy of the old drug molecules is improved by developing new drug delivery systems. These are transdermal drug delivery systems, liposomes, niosomes, mixed micelles, microspheres/nanoparticles, aquasomes, osmotic pump, occuserts, progestaserts, microencapsulation and resealed erythrocytes etc. The idea of delivering drugs through the skin is old, as far back as the 16th century B.C. The Ebers Papyrus recommended that the husk of the castor oil plant be crushed in water and placed on an aching head and the headache will be cured at once, as though it had never ached (Mez-Mangold, 1971).

Today transdermal drug delivery system is a well-accepted means of delivering many drugs to the systemic circulation and currently transdermal patch devices are used to treat
motion sickness, hypertension, angina, female menopause, severe pain states, nicotine dependence and male hypogonadism (Guy, 1996). With the conventional dosage forms, the amount of drug absorbed through GIT varies depending on the quantity and types of food in the stomach, GIT motility, transit time, and GIT microbial flora, which can destroy some agents. In case of drugs with a high hepatic extraction ratio, the absorbed drug may be largely deactivated by first pass metabolism before reaching the systemic circulation. With the transdermal drug delivery system the drug is absorbed from the skin into the capillaries that are under the skin and then into the general circulation (Guy and Hadgraft, 1980).

1.1 TRANSDERMAL DRUG DELIVERY SYSTEMS

1.1.1 Advantages

The perceived advantages for transdermal drug delivery includes (Chien et al., 1989; Guy and Hadgraft, 1980).

1. Avoidance of the risks and inconveniences of intravenous therapy.

2. Transdermal medication delivers a steady infusion of a drug over an extended period of time. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided.

3. Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problem associated with the drug e.g. gastro-intestinal irritation, low absorption, decomposition due to hepatic “first-pass” effect, formation of metabolites that cause side effects, short half-life necessitating frequent dosing etc. Due to above advantages, it is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, if for example the drug given orally.

4. The simplified medication regimen leads to improved patient compliance and reduced inter and intra patient variability.

5. Self-administration is possible with these systems.

6. The drug input can be terminated at any point of time by removing transdermal patch.
7. Less chance of over or under dosing as the result of prolonged, preprogrammed delivery of drug at the required therapeutic rate

1.1.2 Limitations

Apart from these advantages, transdermal drug delivery systems have some limitations (Mishra et al., 1990; Harpin and Rutter, 1983)

1. The drug must have some desirable physicochemical properties for penetration through stratum corneum.

2. Skin irritation or contact dermatitis due to the drug, excipients and enhancers of the drug used to increase percutaneous absorption is another limitation.

3. Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.

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

1.2 CRITERIA FOR SELECTION OF DRUGS

The important criteria in the drug selection for the development of transdermal drug delivery systems can be summarized as follows (Franz et al., 1992).

1. Adequate skin permeability
   - Drugs with low molecular weight.
   - Drugs with low melting point.
   - Drugs with moderate oil and water solubility.
   - Potent drugs.

2. Adequate skin acceptability
   - Non irritating drugs.
   - Non sensitizing drugs.
   - Non metabolizing drugs.
3. Adequate clinical need
   Need to prolong administration.
   Need to increase patient compliance.
   Need to reduce side effects on non-target tissues.

1.2.1 Adequate Skin Permeability (Hadgraft and Guy, 1989)

- Drugs with low molecular weight
  The diffusion of drugs in polymers is more sensitive to molecular size than transport in liquids. Empirical formula to correlate diffusion coefficient (D) with molecular weight (M) is:

  \[
  \log D = -S_m \log M + K_m
  \]

  \(S_m\) and \(K_m\) are constants.
  Drugs contained in the adhesive layer are released rapidly to the skin and will act as a loading dose if the molecular weight of drug is sufficiently low.

- Drugs with low melting point
  In order to obtain the best candidate for transdermal drug delivery system an attempt should be made to keep the melting point of the drug as low as possible.

- Drugs with moderate oil and water solubility (Partition coefficient of the drug)
  The oil-water partition coefficient is an indication of the lipophilic or hydrophilic character of a drug molecule. It is generally expressed as:

  \[
  K = \frac{C_1}{C_2}
  \]

  \(C_1\) and \(C_2\) are the equilibrium concentrations of the substance in solvent 1 (octanol) and solvent 2 (water) when the drug is partitioned between the two in a concentration insufficient to saturate the two solutions.

  Since a drug administered by transdermal route has to traverse through both the lipophilic stratum corneum and much hydrophilic viable epidermis and dermis, it should have moderate solubility both in lipids and water. Passage of drugs through lipid
membranes and interactions with macromolecules at receptor sites sometimes correlate well with the octanol/water

- Potent drugs
  A transdermal system should not cover an area much larger than 50 cm$^2$. Skin is very efficient barrier in the ingress of materials and drugs which are supposed to penetrate skin relatively e.g. Nitroglycerin, do so at fluxes in the 10-15 μg cm$^{-2}$hr$^{-1}$ range, from saturated aqueous solution. Hence the total nitroglycerin delivered across the skin from a 50 cm$^2$ system is one that is approximately 15 mg. In general transdermal drug delivery system is suitable only for those drugs for which the daily dose is of order of few mg.

1.2.2 Adequate Skin Acceptability

- Non-irritating drugs, non-sensitizing drugs
  An important concept is that virtually any chemical including water may qualify as an irritant. This depends largely upon circumstances of exposure to the chemical substance.

  The irritation/sensitization problem is not only limited to the drug substance, but also the components of adhesives in contact with the skin. Constituents such as plasticizers can leach into the epidermis and create difficulties. This may be exacerbated if the system employs solvents like ethanol or penetration enhancers like propylene glycol. These local toxicological effects may be enhanced by the occlusive nature of a patch and by extended contact time of the system with the skin. The long-term effects of putting patches on skin have to be established before formulating new drug entities into transdermal drug system.

- Non-metabolizing drugs
  The skin possesses some ability to metabolize drugs (Kydonieus, 1987 and Tauber, 1982). The contribution of skin metabolism to the elimination of a drug from the body may be relatively small as compared to that in the liver when a drug is administered
systemically. However, the drug candidates selected for transdermal drug delivery system should not be metabolized in the skin.

1.2.3 Adequate Clinical Need (Franz et. al., 1992)

Clinical need is another important area of consideration and possible limitation. Most drugs are adequately administered by oral medication, so it is imperative that an important clinical need be addressed for any proposed transdermal drug delivery system. Of the commercial products available, bypassing the hepatic "first-pass" (inactive metabolites) was the clinical need for nitroglycerin and isosorbide di nitrate systems, extending the duration of activity (t.i.d. versus one patch every 7 days) was needed for clonidine, minimizing toxic side effects (CNS tachycardia, drowsiness, dry mouth) and greater duration of activity (4-6 doses daily versus one patch every 3 days) was needed for scopolamine and bypassing the hepatic first-pass (toxic proteins), minimizing side effects (hypertension, hyperlipidemia, hypercoagulability) and prolongation of duration of activity (one dose daily versus one patch every three to four days) was needed for estradiol.

1.3 SKIN FOR TRANSDERMAL DRUG APPLICATION

The body's first line of defence against the outside world is one of its major organs, the skin. It is water proof, tough, and responds immediately to changes in temperature, sensations of pain and the sensual pleasures of touch. The skin is one of the most extensive and readily accessible organs of the human body. The skin of an average adult body covers a surface area of approximately 2m² (or 3000 inch²) and receives about one-third of the blood circulating through the body. It is elastic, rugged, and under normal physiological conditions, self-regenerating with a thickness of only a few millimeters (2.97 ± 0.28 mm). The skin separates the underlying blood circulating network and viable organs from the outside environment. It serves as a barrier against physical and chemical attacks and shields the body from invasion by microorganisms (Jacob and Francone, 1970).
1.3.1 Anatomy Of Skin

Microscopically the skin is a multilayered organ composed of anatomically many histological layers, but it is generally described in terms of three tissue layers: the epidermis, the dermis, and the subcutaneous fat tissue (Fig 1.1 to 1.3).

- Epidermis
  Histologically the epidermis is composed of keratinizing stratified squamous epithelium. In such a tissue two distinct cellular processes are evident: the replacement of cells continually being lost from the surface, by the mitosis of deeper layers and the transformation of polygonal living cells to dead, flattened scale like structure filled with increasing amounts of the protein keratin, as they age and are removed towards the epithelial surface by the multiplication of the cells beneath them. Considerable variation occurs over the body surface in the rate and extent of these two processes, so that in some regions for example the eye lids, lips and other mucocutaneous junctions the keratinizing layers and indeed the whole epithelium are extremely thin, whilst in others, particularly the palmar and plantar surfaces of the hands and feet, the keratinized layer may be 2 mm or more thick. In general the epidermis of flexor surfaces of the limbs is more delicate than that of extensor surfaces (Waugh and grant, 2001).
  No blood vessels are found in epidermis. It derives its nutrition from lymph. Nerves are found in thin layer. It consists of following layers from outside inward.

a) The stratum corneum
  The stratum corneum (or horny layer) typically comprises 10-15 cell layers and is approximately 10 μm thick when dry (but swells to several times thickness when fully hydrated) Fig 1.4. This membrane, consisting of dead, anucleate, keratinized cells embedded in a lipid matrix is essential for controlling the percutaneous absorption of most drugs and other chemicals. The barrier nature of the horny layer depends critically on its constituents 75-80% proteins, 5-15% lipids, and 5-10% unidentified material on a dry weight basis (Wilkes et al., 1973). The protein fraction predominantly
A. Melanocyte  
B. Muscle  
C. Sebaceous gland  
D. Hair shaft  
E. Epidermis  
F. Dermis  
G. Subcutaneous tissue  
H. Fat  
I. Arterial blood vessel  
J. Sweat gland  
K. Hair follicle  
L. Pacinian corpuscle

Fig 1.1: Cutaway of Human Skin
Fig 1.2: Cross-sectional view of human skin (full thickness)

Fig 1.3: A simplified model of the human skin.
Fig 1.4: Electron micrograph of stratum corneum
comprises α-keratin (approximately 70%) with some β-keratin (10%) and the cell envelope (5%). The lipid constituents vary with body site, the abdomen comprises neutral lipids (75%), sphingolipids (18%), polar lipids (5%), and cholesterol sulfate (2%), (Lampe et al., 1983). Phospholipids are largely absent, a unique feature for a mammalian membrane. The lipid composition of the intercellular domain of the stratum corneum has been well researched (Elias et al., 1977; Elias, 1981; Elias, 1983; Wertz et al., 1989 and Wertz and Downing 1989).

The architecture of the horny layer may be modeled as a brick-and-mortar structure. In this model, the keratinized corneocytes function as a protein "bricks" embedded in a lipid "mortar" (Fig 1.5). The lipid constructs multiple bilayers (Elias et al., 1975 and Grayson and Elias 1982), despite the minimal charged phospholipid content and it has been proposed that there is sufficient amphiphilic material in the lipid fraction such as polar free fatty acids and cholesterol sulfate to maintain a bilayer form (Elias, 1981; Williams and Elias, 1987).

The precise molecular arrangement of intercellular lipid bilayers in horny layer is still being investigated. Lipids covalently bound to the surface of corneocytes may play a part in determining the barrier function of the membrane (Knutson et al., 1986; Potts, 1989; Wertz and Downing 1989). Additionally protein molecules may be intrinsically incorporated into the lipid bilayers (White et al., 1988 and Barry, 1991).

b) *The stratum lucidum*

This is present immediately below the first layer and is a thin, more or less transparent layer in which the cells are indistinct.

c) *The stratum granulosum*

This is the next layer formed by a few layers of large flattened cells, filled up with granules, which stain deeply with haematoxylin. These granules are composed of keratohyalin (eleidin). Due to presence of these granules this layer is called stratum granulosum. Sulphydryl groups, glycogens and phospholipids are found in the cells of this layer.
Fig 1.5: The "brick-and-mortar" model of the stratum corneum.
d) The malphighian layer (Rete mucosum)

This layer is broad and thick and is made up of large cells. Some of the cells appear to be branched and the branches of the adjoining cells run together. Due to this character these cells are called "prickle" cells. These "prickles" are in fact cytoplasmic protrusions and the branches from two cells that actually do not join but stay side by side. The cells in deepest layer of rete mucosum contain granules of the pigment called melanin. They are called melanoblasts. The viable epidermis is about 100 μm thick (Banker and Rhodes, 1979).

- Dermis (cutis vera or corium)

This layer is made up of the following parts:

a) Large cells belonging to the reticuloendothelial system. Histocytes called melanophores found in this region may contain melanin but do not synthesize them.

b) Fine elastic fibres.

c) Capillary blood vessels and lymphatic: The blood vessels of the skin form a capillary network in the corium and send out loops of vessel into each papilla. From the corium finger like processes pass outwards and occupy the spaces between similar processes, which descend from rete mucosum. These projections of the dermis are called papilla.

d) Sensory nerve endings of various types.

e) Hair roots or the hair follicles.

f) Sweat glands.

g) Sebaceous glands.

h) Involuntary muscle fibres: These are found in two-forms (1) in the scrotum, penis, nipple and its areola involuntary muscle fibres are found in the deeper portion of dermis (2) arrector pili. These are small bundles of involuntary muscle fibres, which are attached to the hair follicle and pass out into the more superficial portion of corium on that side to which the hair slopes. Except palms and soles, the hair follicles
are distributed all over the skin. Although they are epidermal structures, yet they grow deeper into the dermis. The hair follicles are the small pits in which the hair roots are embedded. The sebaceous glands open at the root of those hair follicles. The sweat glands are composed of single coiled tube, opening directly on the surface. The hair roots are surrounded by sensory nerve endings (Chatterjee, 1994). The dermis is about 0.2 to 0.3 cm thick (Banker and Rhodes, 1979).

- Subcutaneous tissue
  This is a sheet of fat-containing areolar tissue, known as the superficial fascia, attaching the dermis to the underlying structures.

1.3.2 Biochemistry Of The Skin

- Keratinization of the skin
  Histochemical tests indicate that in the region of the granular layer of normal human skin there is a high-energy system responsible for the synthesis of keratin from polypeptides in the cytoplasm of epidermal cells. Sulphydryl groups, phospholipids, and glycogen are concentrated in the granular layer and all are absent in the immediately overlying keratin. At this site the polypeptide chains are presumably unfolded and broken down and resynthesized into keratin molecules (Bell et al., 1963).

- Skin surface lipids
  Sebum, the product of the sebaceous glands, is reportedly a mixture of triglycerides, free fatty acids, waxes, sterols, squalene, and paraffins. The free fatty acids give sebum bactericidal and fungicidal activities. Sebum is produced most abundantly on the forehead, less on the trunk, and none, or very little, on the extremities (for instance, the palms have no sebaceous glands). Sebaceous activity is stimulated by androgens and increases at puberty. It is greater in the second half of the menstrual cycle than the first half, but is very low during pregnancy (Bell et al., 1963).

  In addition to sebum, the skin surface lipids also contain a noncollagenous, fucosylated
glycoprotein, which is an s-s-linked aggregates released by human skin fibroblasts (Sears et al., 1976). The proliferation of human fibroblasts is increased 10 to 20 fold with the addition of human epidermal growth factor (Carpenter and Cohen, 1976). This growth stimulation depends on the presence of serum and is enhanced by the addition of ascorbic acid.

- Skin fatty acids

Skin contains two essential unsaturated fatty acids: linoleic acid and arachidonic acid. Linoleic acid has been identified, as playing an important role in regulating the barrier functions of the skin. On the other hand, arachidonic acid may act to furnish prostaglandins (Hartop and Prottey, 1976).

1.3.3 The Skin Circulatory System

The arteries of the skin are derived from vessels in the subcutaneous connective tissue layer, which form a tangential arterial plexus just beneath the dermis. Branches from this network provide the blood supply to the hair follicles, glandular skin appendages and the subcutaneous fat as well as the dermis itself (Fig 1.6).

The blood supply reaches within some 150 or 200 μm of the skin's outer surface, which means that chemicals gaining access to the body from the skin's surface are picked up and systematically diluted at a depth estimated to average about 200μm. At room temperature (~23°) the blood flow rate to skin is of the order of 0.05 mL/min. per cubic centimeter of the skin.

Elasticity of stratum corneum is dependent upon a proper balance of lipids, hygroscopic water-soluble substances and water in conjunction with keratin proteins. Water is the principle plasticizer and in 10-20% concentration it maintains adequate pliability. The hygroscopic substances or the "natural moisturizing factor" consists of amino acids, urea, inorganic ions and also to some extent stratum corneum lipids. It reacts with stratum corneum proteins to stabilize its mosaic filamented matrix and that it allows relatively efficient binding of plasticizing water. In effect the water makes the tissue less "crystalline" by occupying spaces
Fig 1.6: Vascular Supply to Skin
between polymer molecules. In the absence of adequate moisture, the skin chaps, cracks and splits under stress, pH of the superficial stratum corneum layer is found to be between 4.2 and 5.6. (Woodburne, 1965).

1.3.4 Skin Appendages

Hair follicles and their associated sebaceous glands (pilosebaceous glands), eccrine glands, apocrine glands, and nail plates are referred to as the skin appendages. Hair follicles are found within the skin everywhere except the soles, the palms, the red portion of the lips and the external genitalia. They are formed from epidermal cells in fetal life (Wilkes et al., 1973). A hair (hair shaft) emerges from each follicle. The follicle itself lies within the skin and consists of concentric layers of cellular and noncellular components positioned in the skin at a slight angle. Each follicle is anchored to the surrounding connective tissue by an individual strand of smooth muscle, the arrector pilorum, contraction of which causes the hair to stand upright, raising goose pimples on human skin.

The hair shaft is formed continuously by cell division, differentiation and compaction within the bulb (base) of each active hair follicle, a process that is completed deep in the follicle. Hair, like stratum corneum, is thus a compact of fused keratinized cells. Collectively, hair follicles occupy about 1/1000 of the skin's surface (10.15), a factor that sets a limit on the role they can play as a route of penetration (Scheuplein and Bank, 1967; Sazbo, 1962).

Ecrine or salty sweat glands are found over the entire body except the genitalia of fetal epidermal origin. They consist of tubes extending from the skin surface to the footings of the dermis. Here the tube coils into a ball roughly 100 μm in diameter and by anatomical count, there are between 150 and 600 glands per cubic centimeter of body surface, depending on site. They are particularly concentrated in the palms and soles, attaining densities in these locations well in excess of 400 glands per centimeter (Woodburne, 1965).

Apocrine glands have highly regionalized locations and are found only in the axillae (arm pits), in anogenital regions and around the nipples. Along with other secondary sexual characteristics, the glands develop at puberty. (Wilkes et al., 1973).
1.4 **PERCUTANEOUS ABSORPTION**

When a drug system is applied topically, the drug diffuses passively out of its carrier or vehicle and depending on where the molecules are placed down, it partitions into either the stratum corneum or the sebum-filled ducts of the pilosebaceous glands. Inward diffusive movement continues from these locations to the viable epidermal and dermal points of entry. In this way, a concentration gradient is established across the skin up to the outer reaches of the skin’s microcirculation, where the drug is swept away by the capillary flow and rapidly distributed throughout the body. The events governing percutaneous absorption following application of a drug in a thin, vehicle film are illustrated in Figure 1.7.

Two principal absorption routes are indicated in the sketch: a) the transepidermal route, which involves diffusion directly across the stratum corneum; and b) the tranfollicular route, for which diffusion is through the follicular pore. Since percutaneous absorption is a spontaneous, passive diffusional process that takes the path of least resistance. Therefore, depending on the drug in question and the condition of the skin, either or both routes can be important (Scheuplein and Bank, 1971).

1.5 **CONCEPTUAL ORIGIN OF TRANSDERMAL DRUG DELIVERY**

The potential of using the intact skin as a port of drug administration has been recognized for several decades, as evidenced by the development of medicated plasters. Historically, the medicated plaster can be viewed as the first development of transdermal drug delivery. It is designed to bring medication into close contact with the skin, so drug can be delivered transdermally.

To date, the historical development of medicated plasters has not been well documented. However, the use of medicated plasters can be traced several hundreds years back to ancient China.

Medicated plasters are also very popular in Japan as over-the-counter pharmaceutical dosage forms. They are also commonly called cataplasms. Salonpas, contain multiple
Dissolution of drug in vehicle

Diffusion of drug through vehicle to skin surface

Transepidermal route

Partitioning into stratum corneum

Diffusion through protein-lipid matrix of stratum corneum

Tranfollicular route

Partitioning into sebum

Diffusion through lipids in sebaceous pore

Partitioning into viable epidermis

Diffusion through cellular mass of epidermis

Diffusion through fibrous mass of upper dermis

Capillary uptake and systemic dilution

Fig 1.7: Events governing percutaneous absorption
ingredients, including six purified therapeutically active agents. Medicated plasters have also been available in Western medicine for several decades. For example, Allock's porous plasters of England and the ABC (arnica/belladonna/capsicum), plaster of Germany. In the United States, three medicated plasters have been listed in the official compendia since early as 40 years ago: belladonna plaster, mustard plaster, and salicylic acid plaster. Like the oriental plasters, the Western medicated plasters are rather simple in formulation and were developed mainly for local medication.

1.5 COMPONENTS OF TDDS

Transdermal drug delivery system (TDDS) generally include following basic components:

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<th>Backing substrate</th>
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<td>Drug reservoir component</td>
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<tr>
<td>Control membrane</td>
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<tr>
<td>Contact adhesive</td>
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<td>Release liner</td>
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➢ Backing substrate: Is an impermeable substrate that protects the product during use on the skin.

➢ Drug reservoir component: Is an adhesive layer containing most of the system's drug.

➢ Control membrane: A polymeric film that controls the rate at which the drug leaves the system and enters the body.

➢ Contact adhesive: A hypoallergenic adhesive designed to hold the product next to the skin for desired length of time.

➢ Release liner: A plastic substrate that protects the product in the package. The user discards the liner when applying the system.

Desired attributes for critical materials used for transdermal drug delivery system
1.6.1 Backing Substrate

Backing films must be flexible, they must provide good bond to the drug reservoir, prevent drug from leaving the dosage form from the top and accept printing. Metal foils, paper, polyesters, polyvinyl chloride, nylon, non-wovens, fabrics etc. are considered to be the suitable candidates for backing substrate.

1.6.2 Drug Reservoir Component

Drug reservoir component must be compatible with drug and must allow the drug transport at the desired rate. If an ointment, the drug reservoir must possess desired viscosity attributes to ensure a reliable manufacturing process. If an adhesive, the drug reservoir must possess the desired adhesive and cohesive properties to hold the system together. The drug is dissolved or distributed uniformly throughout the matrix after adsorbing it many times into a suitable adsorbent like lactose (Guy and Hadgraft, 1987).

The matrix components are many, so are the types pressure sensitive adhesive (Zhao et al., 2002), polyurethane (Cal et al., 2001), silicone (Maillardsalin et al., 2000), polyvinyl pyrrolidone and ethylcellulose (Rao et al., 2000), hydroxypropyl methylcellulose (Verma et al., 2000), acrylic polymer (Deog et al., 1999), colloidal dispersions (Andersson et al., 1999), gelatin (Kantaria et al., 1999), polyisobutylene (Janan et al., 1999), poly acrylic acid (Bai et al., 1998), ethylene vinyl acetate (Guillemet et al., 1998), sodium carbomethyl cellulose (Paranjothyl and Thampi, 1997), methacrylate copolymer (Wolff and Christoph, 1997), polyvinyl pyrrolidone and poly ethylene oxide (Feldstein et al., 1996), chitosan (Nah et al., 1996) and gum karaya (Yuk et al., 1996).

The drug candidates evaluated for transdermal drug delivery system have ranged from antihypertensive, antianginal, antihistaminic and anti-inflammatory agents to analgesics, antiarthritic, steroidal and contraceptive drugs. The drugs, which are tried by transdermal route are leuprolide (Georgiso and Charu, 2003), antibiotic peptide bacitracin (Hadgraft et al., 2003), testosterone (Hong et al., 2002), 5-fluourouracil (Fang et al., 2002), methotrexate (Alvarezfigueoa and Mendez, 2001), diclofenac sodium (Dureja et al., 2001), azone
laurocapram (Kanikkannan et al., 2001), apomorphine (Li et al., 2001), heparin (Mitragotri and Kost, 2001), insulin (Shun et al., 2001), estradiol (Chandrasekharan and Fleisher, 2000), salmon calcitonin (Chang et al., 2000), ondansetron hydrochloride (Ding et al., 2000), diltiazem hydrochloride (Blair, 1999), selegiline (Gordon et al., 1999), oxprenolol (Bolgul et al., 1998), ketorolac trimethamine (Devi and Paranjothy, 1998), scopolamine (Braun et al. 1997), timiperone (Takayasu, 1996), indomethacin (Lange et al., 1995), Captopril (Jain et al., 1995), terbutaline (Jain et al., 1992), bromhexine (Thasu and Vyas 1991) and salbutamol (Jain et al., 1990)

1.6.3 Control Membrane

It is polymeric film that controls the rate at which the drug leaves the system and enters the body. Such a control is necessary if the drug penetrates rapidly requiring a device control for the rate of penetration. Rate controlling membranes with tight physical and chemical specifications will ensure reproducible drug release rates among the lots. Transdermal drug delivery systems have been made with micro porous membranes and with dense polymeric membranes.

Polypropylene, alkyl esters of acrylic and methacrylic acids, blend of polyurethane, and N-vinyl pyrrolidone glycidyl methacrylate copolymer, macromer cross-linked grafts polymers prepared by simultaneous copolymerization and cross-linking of 2-hydroxy ethylmethacrylate in presence of polytetramethylene oxide, hydroxypropyl cellulose plus polyethylene glycol plus ethylcellulose, polyamide, polyvinylacetate, a macromer cross-linked graft copolymer synthesized from simultaneous copolymerization, cross-linking of 2-hydroxy ethyl methacrylate in presence polytetra methylene oxide dissolved in appropriate amount of diisocynate, ethylenevinyl alcholol copolymer, acrylic acid-2-ethoxyethyl acrylate iso octyl acrylate copolymer, poly butyl cyanoacrylate and poly hexyl cyanoacrylate etc. in their various combinations have been tried as the possible candidates for control membranes (Good, 1983; Lawson, 1985; Rao and Diwan, 1997; Sun et al., 1997 and Hogson, 1978).
1.6.4 Contact Adhesives

The contact adhesives should be hypoallergenic with desired adhesives and cohesives properties, be skin compatible, and possess desired drug solubility and permeability characteristics. 2-ethyl hexylacrylate, polyvinyl pyrrolidone, rubber based pressure sensitive adhesives, polyvinyl alkyl ether pressure sensitive adhesives and the acrylate pressure sensitive adhesives, acrylonitriles and elastic adhesives have been commonly employed for this purpose.

1.6.5 Release Liner

The release should permit easy peel by the user and yet should not interfere with functionality of the product. The cost must be compatible with the concept that the liner is thrown away. Siliconized paper or teflon sheets are used as released liners.

1.6.6 Packing Substrate

The packing substrate should be moisture barrier, ensure product stability and have an easily printable outer surface.

1.7 System Designs for Transdermal Drug Delivery

Several system design capable of providing rate-controlled release of drugs have been used in the development and fabrication of transdermal drug delivery system (Chien, 1987 and Chein, 1992). Each of these designs aims to facilitate the release of drug at a specific rate. The system designs, that have been introduced in the market can be classified into the following five basic types:

1.7.1 Reservoir Type

The transdermal drug delivery system consists of a drug reservoir sandwiched between a rate-controlling polymeric membrane and a drug-impermeable backing laminate (Fig 1.8). In the drug reservoir compartment the drug solids are either dispersed homogeneously in a solid polymer matrix (e.g. poly isobutylene adhesive) or suspended in an unbleachable viscous
liquid medium (e.g. silicone fluid) to form a paste like suspension. The rate controlling membrane can either be a microporous or nonporous polymeric membrane (e.g. ethylene vinyl acetate copolymer) with defined drug permeability. On the external surface of the polymeric membrane, a thin layer of drug compatible hypoallergenic pressure sensitive polymer (e.g. silicone or poly isobutylene adhesive) may be applied to provide an intimate contact of transdermal therapeutic system with the skin surface. The rate of drug release from this type of transdermal drug delivery system can be tailored by varying the polymer composition, the permeability coefficient and/or the thickness of rate controlling membrane and an adhesive.

Marketed transdermal products that have used the reservoir-type design to achieve rate-controlled release include the Transderm-Nitro system (nitroglycerin) for angina pectoris, the Estraderm system (estradiol) for estrogen replacement therapy, the Androderm system (testosterone) for hypogonadism and the Duragesic system (fentanyl) for the management of chronic pain.

1.7.2 Drug-In-Adhesive Type

The drug-in adhesive transdermal drug delivery system is a simplified system in which the drug is dispersed in an adhesive polymer (e.g. poly isobutylene or poly acrylate) Fig 1.9. The medicated adhesive is spread by solvent casting or hot melts on to the flat sheet of the drug impermeable backing support to form one or more layers of drug reservoirs. On the top of the drug reservoir layer thin layer of non-medicated rate controlling adhesive polymer of specific permeability may be applied to produce a transdermal drug delivery system.

Alternatively this type of transdermal drug delivery system can be modified to have the drug loading level varied at increment to form a gradient of a drug reservoir along the multilaminate adhesive layers. Examples of currently marketed system that use this design include Climara (estradiol), Mintrane (nitroglycerin), Habitrol (nicotine) and Nicotrol (nicotine).
1.7.3 Matrix Type

The drug reservoir in this type of TDDS is made by dispersing the drug into a hydrophilic or a lipophilic polymer makes the drug reservoir in this type of transdermal drug delivery system. This polymeric matrix modulates the release of the drug and thus function as the rate-controlling medium. The medicated polymer is molded into a disc with a well-defined drug releasing area and thickness. The medicated polymer is mounted onto an occlusive base plate made from a drug-impermeable backing (Fig 1.10). An adhesive polymer is applied along the circumference of the drug-releasing disc to form an adhesive rim surrounding the transdermal drug delivery system.

The ProStep system uses a hydrogel to form the polymer matrix to provide the rate control release of the nicotine for smoking cessation therapy, whereas Nitrodisc uses a lipophilic elastomer to form the polymer matrix to modulate the release of nitroglycerin for the treatment of angina.

1.7.4 Membrane-Matrix Hybrid Type

The membrane-matrix hybrid type transdermal drug delivery system is essentially a modification of the reservoir-type transdermal drug delivery system. The liquid type formulation of the drug reservoir is replaced with a solid polymer matrix (e.g. poly isobutylene) that is sandwiched between the rate controlling membrane and the drug- impermeable backing laminate. Thus, this transdermal drug delivery system differs from the reservoir type only in the composition of the reservoir (Fig 1.11). With this system design, drug permeation may be controlled by the rate controlling membrane and/or the polymeric matrix, depending on the duration of application and the physicochemical properties of the drug- reservoir and the membrane. The drug release profile obtained from these systems can be monophasic, biphasic or triphasic. Several of these transdermal products have been marketed, including the Transderm-Scop system (Scopolamine) for the prevention of the motion sickness, the Catapres-TDDS system (clonidine) for the treatment of hypertension, and the Nicoderm system (nicotine) for smoking cessation therapy.
Fig 1.8: Reservoir type transdermal drug delivery system.

Fig 1.9: Drug-in-adhesive transdermal drug delivery system

Fig 1.10: Matrix - type transdermal drug delivery system
1.7.5 Microreservoir Type

The microreservoir type transdermal drug delivery system is a combination of the reservoir type and the matrix-type transdermal drug delivery system (Fig 1.12). The drug reservoir is formed by first suspending the drug solids in an aqueous solution of water-miscible drug solubilizer e.g. polyethylene glycol. A high-shear mechanical force in a lipophilic polymer forming thousands of unetectable microscopic drug reservoirs (microreservoirs) homogeneously disperses the drug suspension. This dispersion is quickly stabilized by immediately cross-linking the polymers chain in situ which produces a medicated polymer disk of a specific area and a fixed thickness. An occlusive base plate mounted between the medicated disc and adhesive foam backing prevents loss of drug through the backing. The Nitrodisc system currently marketed for the treatment of angina pectoris is an example of microreservoir drug delivery system.

1.8 ADVANCES IN TRANSDERMAL CONTROLLED DRUG DELIVERY

The drug candidates evaluated for transdermal administration include antihypertensive, antianginal, antihistamine, anti-inflammatory, analgesic, antiarthritic, steroids and contraceptives. It has been estimated that within the next few years over 10% of drug products will be marketed in transdermal drug delivery system. On the other hand, it has been increasingly recognized that not every drug can be delivered transdermally at a rate high enough to achieve blood level that is therapeutically beneficial for systemic medication.

To achieve and maintain a plasma drug concentration above the minimum therapeutic level, the barrier properties of the skin must be overcome for the effective transdermal controlled delivery of drugs. The following approaches have been shown to be potentially promising for accomplishing the goals of reducing skin’s barrier and enhancing the transdermal permeation of drugs:
Fig 1.11: Microreservoir-type transdermal drug delivery system

Fig 1.12: Multilaminate drug-in-adhesive transdermal drug delivery
1. Physical approach
   A. Stripping of stratum corneum
   B. Hydration of stratum corneum
   C. Iontophoresis
   D. Sonophoresis
   E. Phonophoresis
   F. Thermal energy

2. Chemical approach
   A. Synthesis of lipophilic analogs
   B. Delipidization of stratum corneum
   C. Co-administration of skin permeation enhancer

3. Biochemical approach
   A. Synthesis of bioconvertible prodrugs.
   B. Co-administration of skin metabolism inhibitors.

1.9 KINETICS OF TRANSDERMAL PERMEATION

Knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic systems. Transdermal permeation of a drug involves the following steps:
1. Sorption by stratum corneum,
2. Penetration of drug through viable epidermis,
3. Uptake of the drug by the capillary network in the dermal papillary layer.

The rate of permeation across the skin \( \frac{dQ}{dt} \) is given by (Chien, 1982):

\[
\frac{dQ}{dt} = P_S \left( C_d - C_r \right)
\]

\( C_d \) - concentration of skin penetrates in the donor compartment
\( C_r \) - concentration in the receptor compartment
\( P_S \) - over all permeability of the skin tissues to the penetrant.
This permeability coefficient is given by the relationship:

\[ P_s = \frac{K_S D_{SC}}{h} \]

\( K_S \): the partition coefficient for the interfacial partitioning of the penetrant molecules from a solution medium or a transdermal therapeutic system on to the stratum corneum.  
\( D_{SC} \): the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues.

Since \( K_S, D_{SC}, \) and \( h \) are constant under given conditions, the permeability coefficient \( (P_S) \) for a skin penetrant can be considered to be constant. From equation it is clear that a constant rate of drug permeation can be obtained only when \( C_o \gg C_r \), i.e., the drug concentration at the surface of the stratum corneum \( (C_o) \) is consistently and substantially greater than the drug concentration in the body \( (C_r) \). Then equation becomes:

\[ \frac{dQ}{dt} = P_s C_o \]

and the rate of skin permeation \( (dQ / dt) \) is constant provided the magnitude of \( C_o \) remains fairly constant throughout the course of skin permeation. For keeping \( C_o \) constant, the drug should be released from the device at a rate \( (R_o) \) that is either constant or greater than the rate of skin uptake \( (R_s) \) i.e., \( R_o \gg R_s \).

Since \( R_o \) is greater than \( R_s \) than the drug concentration on the skin surface \( (C_o) \) is maintained at a level equal to or greater than the equilibrium or saturation solubility of the drug in the stratum corneum \( (C_S) \) i.e., \( C_o \gg C_S \). Therefore, a maximum rate of skin permeation \( [(dQ / dt)_{max}] \) is obtained and is given by the equation:

\[ [(dQ / dt)_{max}] = P_s C_S \]

The maximum rate of skin permeation depends on the skin permeability coefficient \( (P_S) \) and its equilibrium solubility in the stratum corneum \( (C_S) \). Thus skin permeation appears to be stratum corneum limited (Sanvordekar, 1982).
1.10 EVALUATION OF TRANSDERMAL SYSTEMS

1.10.1 In Vitro Evaluation Of Transdermal Drug Delivery System

The design and development of transdermal drug delivery systems is greatly aided by in vitro studies. In vitro studies can help in investigating the mechanisms of skin permeation of the drug before it can be developed into a transdermal therapeutic system and optimize the formulation before more expensive in vivo studies are performed. Ideally, an in vitro system should be designed in such a way that the intrinsic rate of release or permeation, which is theoretically independent of the in vitro design, can be accurately determined. A well-designed in vitro apparatus assures that the mechanism of drug delivery is truly from the transdermal drug delivery system. Several designs of the in vitro membrane permeation apparatus are in existence. These include the Valia Chein (V-C) skin permeation cell, Ghannam Chein (G-C) membrane permeation cell, Franz diffusion cell, Keshary Chein (K-C) skin permeation cell and Jhawer - Lord (J-L) rotating disc system (Fig 1.13 to 1.17). The most widely used of these are the Franz diffusion cell and the K-C cell.

1.10.2 In Vivo Evaluation Of Transdermal Drug Delivery System

In vivo evaluation of transdermal drug delivery systems can be carried out using:

- Animal models
  In vivo animal models are preferred because considerable time and resources are required to carry out studies in humans. Some of the species that have been used both for in vivo and in vitro testing include mouse, rat, guinea pig, rabbit, hairless mouse, rat, dog, cat, miniature pig, pig, horse, goat, squirrel, monkey, rhesus monkey and chimpanzee.

- Human models
  The final stage in the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the device to human volunteers. An in vivo evaluation using human subjects should give pertinent
Fig 1.13: Valla-Chien (V-C) Skin Permeation Cell
Fig 1.14: Ghannam-Chien (G-C) Membrane Permeation Cell

Fig 1.15: Franz Diffusion Cell
Fig 1.16: Keshany - Chien (K-C) Skin Permeation cell

Fig 1.17: Jhawer-Lord (J-L) Rotating - Disk System
information with minimum risk to the subjects within a reasonable period of time. Procedures for *in vivo* evaluation in human beings were first described by Feldmann and Maibach (Maibach and Feldman, 1969; Feldman and Maibach, 1974). They involve determination of percutaneous absorption by an indirect method of measuring radioactivity in excreta following topical application of the labelled drug. This method is used since plasma levels following transdermal administration of a drug are too low to use chemical assay procedures.

• Biophysical models

Models based on steady-state mass balance equation, solution of Fick's second law of diffusion (with appropriate conditions) for the device, stratum corneum and viable epidermis (Guy and Hadgraft, 1980; Albcry et al., 1983; Hadgraft, 1979; Guy and Hadgraft, 1982) as well as linear kinetics (Guy and Hadgraft, 1982, 1984; Guy et al., 1985; Guy and Hadgraft, 1985) have been described in the literature. An effective model permits investigation of experimentally inaccessible or poorly defined variables of the percutaneous absorption process. Examples, which have already been dealt with, include cutaneous metabolism (Guy and Hadgraft, 1984; Wester et al., 1983) and effect of penetration enhancers.

• Cutaneous toxicological evaluations

An important part of the evaluation of transdermal drug delivery systems pertains to the deleterious effects they have on the skin. While there have been significant advances in the evaluation of transdermal systems for cutaneous toxicology, the enormous range of structural and functional capacity of skin from one individual to another compounds the difficulty in assessing the potential adverse effects a transdermal system may have on the skin.
• Contact irritant dermatitis

Contact irritant dermatitis results from direct toxic injury to cell membranes, cytoplasms or nuclei. This is generally manifested by inflammation, cutaneous erythema and itching and can occur from the drug, vehicle, absorption enhancers and from the adhesive used to secure the system. Screening of new systems for contact irritant dermatitis involves use of animals like rabbits or guinea pigs. A major part of the screening deals with testing in humans.

• Contact allergic dermatitis

Contact allergic dermatitis involves a host immunological reaction to an antigen. The antigen is viewed to be a complex between an externally applied compound and skin proteins. The most widely accepted and useful test for screening systems for contact allergic dermatitis is the guinea pig maximization test (Magnusson, 1969).
1.11 TRANSDERMAL FORMULATIONS

The transdermal formulations for wide variety of products available are summarized below (Khali and Sen, 1997):

<table>
<thead>
<tr>
<th>Category / Product</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Metabolic / GIT</td>
<td>Elan&lt;br&gt;Alza, Cheil, Hercon, Ciba Geigy</td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td></td>
</tr>
<tr>
<td>Scopolamine</td>
<td></td>
</tr>
<tr>
<td>B. Cardiovascular</td>
<td>Alza, Elan, Hercon, Boehringer Ingelheim&lt;br&gt;Beiersdorf, Elan, Hercon, Moleculon, Alza, Elan, Forest, Searle, Nippon Kayaku, Key, Hercon, 3M Riker, Schwarz, Beiersdorf</td>
</tr>
<tr>
<td>Clonidine</td>
<td></td>
</tr>
<tr>
<td>Isosorbide Dinitrate</td>
<td></td>
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<tr>
<td>Nitroglycerine</td>
<td></td>
</tr>
<tr>
<td>C. Genitourinary</td>
<td>Ciba Geigy&lt;br&gt;Alza, Hercon, Moleculon, Pharmed, 3M Riker&lt;br&gt;Alza, Hercon</td>
</tr>
<tr>
<td>Estradiol and Norethisterone</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td></td>
</tr>
<tr>
<td>D. Musculoskeletal</td>
<td>Cheil&lt;br&gt;Kowa</td>
</tr>
<tr>
<td>Diclofenac</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td></td>
</tr>
<tr>
<td>E. Respiratory</td>
<td>Pierre Fabre&lt;br&gt;Ciba Geigy, Alza, Moleculon, 3M Riker, Elan</td>
</tr>
<tr>
<td>Salbutamol</td>
<td></td>
</tr>
<tr>
<td>Nicotine</td>
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</table>

1.12 RESEARCH ENVISAGED AND PLAN OF WORK

Hypertension is the most important risk factor underlying cardiovascular morbidity and mortality in industrialized countries. Hypertension is the major factor that leads to 1,500,000 heart attack and 567,000 heart attack deaths per year in USA. Therefore, the treatment of hypertension, reduces the incidence of cardiovascular morbidity and mortality. This treatment should be effective and well tolerated to improve the patient’s quality of life.
The drug Atenolol / Metoprolol tartrate are widely recognized and extensively prescribed as first choice of drugs in the treatment of majority of the hypertension population. The conventional formulation of these drugs is rapidly dissolved in upper gastric intestine and produces peak plasma concentration within 1 to 4 hours and then decline quickly. Consequently, divided doses are recommended for maintaining the effective plasma concentration. However, conventional formulations exhibited following drawbacks:

- Produces peaks and valley time drug plasma concentration on multiple dosing of conventional formulation of Atenolol and Metoprolol tartrate.
- Multiple dosing results in high and rapid plasma concentrations after each dose, which may be associated with undesirable beta-2 mediated effects like fatigue and bronchospasm.
- The conventional formulations fail to provide adequate protection against myocardial ischemic episode, which shows circadian pattern.
- Arterial blood pressure also exhibits circadian rhythm that leads to serious cardiac problems that occurs during early morning hours. Adequate 24- hours control of blood pressure may not be provided by the conventional formulations.
- The short half-life of the conventional formulations necessitates the multiple dosing which may lead to blood pressure variation over 24-hours and hence may increase target organ damage.
- Atenolol / Metoprolol tartrate are subjected to first-pass metabolism, which increases the dose size of the drug.

All the drawbacks necessitate the development of an even and effective drug delivery system which could maintain the drug plasma concentration throughout 24 hours in order to achieve maximal cardio protection, improved patient compliance, maximal drug utilization and enhanced bioavailability.

Therefore, large area and easy accessibility of the skin was utilized for constant and controlled delivery of Atenolol / Metoprolol tartrate. The development of transdermal drug delivery system bearing Atenolol / Metoprolol tartrate could protect drug from first hepatic pass degradation and maintain a constant drug plasma level for extended period of time.
This could maximize the drug utilization, improve bioavailability of drug and exhibit better patient compliance.

Further, the matrix diffusion controlled drug delivery system was designed and developed for controlled delivery of Atenolol / Metoprolol tartrate because of ease of fabrication and cost effective.

The present work was undertaken under following lines:

➢ Drug analysis: Establishing the estimation process of Atenolol / Metoprolol tartrate in buffers and biological fluids.

➢ Preformulation studies: The preformulation studies included solubility, partition coefficient, drug metabolism, skin permeability, interference with additives, preparation and evaluation of polymeric free films.

➢ Development of matrix diffusion controlled transdermal drug delivery of Atenolol / Metoprolol tartrate systems and their physico-chemical characterization.

➢ In vitro evaluation of matrix diffusion controlled transdermal drug delivery system for drug release from the system and skin permeation of drug.

➢ Stability studies as per ICH guidelines.

➢ In vivo evaluation by periodic measurement of drug plasma level.

➢ Skin irritation studies.
REFERENCES


Marcel Dekker Inc, New York, 341.


[Handwritten note: Red! Iron! Modified!]

Note: The handwritten note appears to be referring to the use of red iron solutions or modifications, but the context is not clear from the text provided.