CHAPTER-1

INTRODUCTION

1.1 Controlled release drug delivery systems- an emerging aspect in effective drug release:

A dosage form can be defined as the means of containing and delivering the drug(s) for its local and/or systemic bioavailability. Dosage forms for releasing the drug(s) can be divided broadly into two types- conventional dosage forms and controlled release dosage forms. The fundamental of controlled release drug delivery system is to optimize the biopharmaceutics, pharmacokinetic and pharmacodynamic properties of drug in such a manner that its utility is maximized by controlled release of the drug and by reducing the side effects [1]. Formulation of controlled release drug delivery systems involves the inevitable application of polymers which control the release of drug in the systemic circulation and maintain plasma drug level within the therapeutic range for a longer period. The ways in which chemicals or drugs are administered have gained increasing attention in the past two decades. Normally, a chemical is administered at a given time only and repeat that dose after several hours or days later. This is not economical and sometimes results in damaging side effects. As a consequence, increasing attention has been focused on methods of administering drugs continually for prolonged time periods and in a controlled fashion. The primary method of accomplishing this controlled release has been through incorporating the chemicals within polymers. This technology now spans many fields and includes pharmaceuticals, food and agricultural applications, pesticides, cosmetics, and household products. In the pharmaceutical field, in addition to the importance of polymers, an understanding of the physiological barriers in the human body is also critical to develop appropriate controlled release systems. The skin, the gastrointestinal tract, the nose and the eye are of particular importance.

The strategies used by the pharmaceutical industry for discovery of a potential new drug delivery system have been changed dramatically in recent year. These changes in strategy present new challenges and opportunities for the application of new methodologies in the drug delivery processes. The study of the controlled release of drug for their extended and safe use has become an important field of research and drug delivery to the systemic circulation through the intact skin has been considered as an important route of drug delivery. Large numbers of drugs are successfully used in this

particular route. Formulations applied on skin can be classified into two categories according to the target site of action of the containing drugs. One has systemic action after drug uptake from the cutaneous microvascular network and the other exhibits local effects in the skin [2]. Typically all conventional dosage forms with the lone exception of I.V. infusion follow first order kinetics with respect to release of drugs from the dosage form. This means the dosage form release the drug initially at a faster rate thus leading to quick raise in blood level of the drug and then falls exponentially until a further dose is administered. This results in peaks and valleys pattern in drug concentration in blood. Thus for most of the time the drug is above the required therapeutic level or below it. Equality in rate of absorption and the rates of metabolic elimination could result in equilibrium distribution of drug delivery system or therapeutic system. Essentially the advent of drug delivery systems brings rate controlled delivery with fewer side effects, increased efficacy and constant delivery.

1.2 Transdermal drug delivery systems:

During the last decade, transdermal delivery of drugs has received increasing attention in the face of growing awareness that administered by conventional means are frequently excessively toxic and sometimes ineffective. Thus, conventionally administered drugs in the form of pills, capsules, injectables, and ointments are introduced into the body as pulses that usually produce large fluctuation of drug concentration in the bloodstream and tissues and, consequently, unfavorable patterns of efficacy and toxicity.

As shown in figure 1.1, transdermal delivery affords an improved approach to the administration of drugs by maintaining a therapeutic but constant concentration of drug in the blood for a desired period of time, usually between 1 and 7 days. Theoretically, the two most important advantages of transdermal delivery are (1) reduction of side effects due to optimization of the blood concentration-time profile; and (2) extended duration of activity, which allows greater patient compliance owing to elimination of multiple dosing schedules [3]. Transdermal delivery may also increase the therapeutic value of many drugs by obviating specific problems associated with the drug, e.g., gastrointestinal irritation, low absorption, decomposition due to hepatic "first-pass" effect, formation of metabolites that cause side effects, and short half-life necessitating frequent dosing.

The choice of drugs to be delivered transdermally is a most difficult task, and careful consideration should be given to each application before large expenditures are committed to clinical testing. Currently only a few drugs could be delivered transdermally, owing to three basic limitations: inadequate permeability through skin, inadequate tolerability of the drug by the skin, and clinical need. The stratum corneum layer of the skin is an exceptionally effective barrier to most chemicals, including drugs.

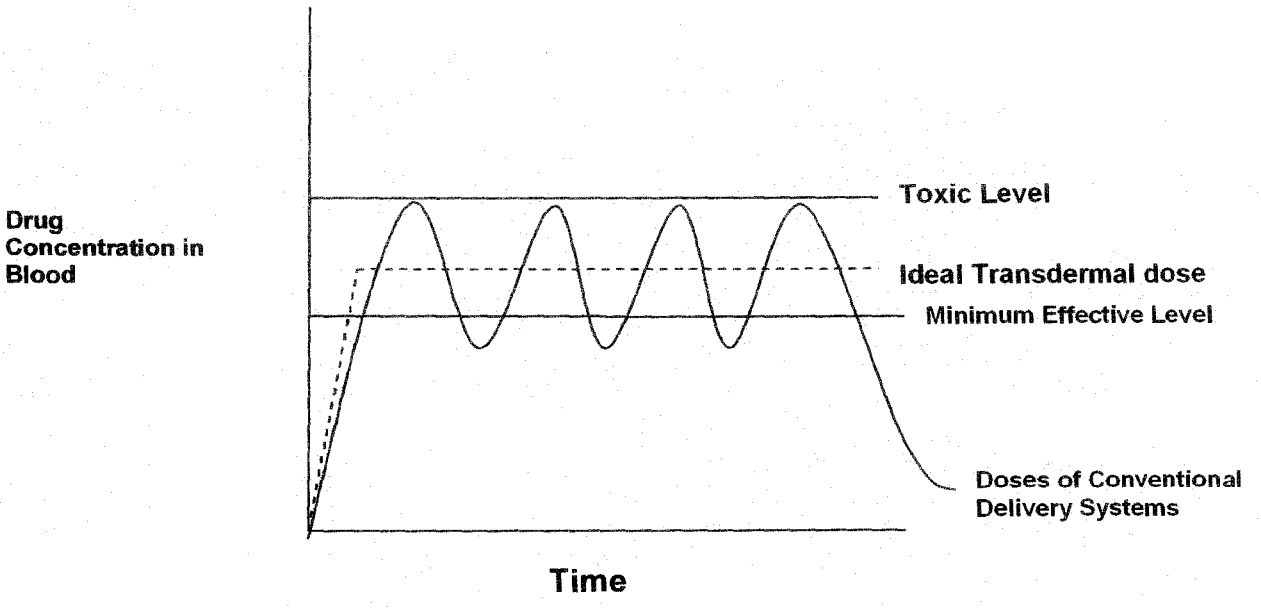


Figure 1.1: Graphical presentation of plasma drug level after conventional and controlled delivery:

Thus very few drugs can permeate this horny layer in amounts sufficient to deliver a therapeutic dose. Fortunately, skin permeation models and adequate experimental data exist that allow one to make a reasonable prediction of a drug's permeability through skin. Chemical and nonchemical enhancers used to increase permeation exacerbate the skin's

tolerability of the drug and enhancers. We now appreciate that the skin performs a variety of tasks that maintain a homeostatic balance between the "inside" of the body and the "outside" environment. Tasks significant in transdermal delivery include regulation of heat and water loss (hydration, occlusion), resistance to mechanical stress (ultrasonic enhancement), and protection of the host from toxic materials (drugs, enhancers). Protection of host from drugs and enhancers comes in the form of skin irritation and sensitization. Skin irritation (or contact irritant dermatitis) results from the direct toxic injury to cell membranes, cytoplasm, or nuclei. To repair the damage, the arachidonic acid cascade is initiated through which the lipoxygenase and cycloxigenase pathways produce very potent inflammatory chemicals, such as leukotrienes, prostaglandins, and thromboxanes. Skin sensitization, or contact allergic dermatitis, involves mainly a host immunologic activity which is mediated by the different types of skin cells, e.g. keratinocytes, langerhans, macrophages, and mast cells, which can synthesize a variety of cytokines and other bioactive materials that are responsible for the local skin immune reaction and systemic immune responses. It is expected that over 80 % of all drugs will have significant irritation or sensitization problems.

In addition to skin, drug and drug-skin interaction, drug pharmacokinetic and design of the transdermal delivery device are also very important. In transdermal drug delivery, pharmacokinetics is important because target tissues are seldom directly accessible, and drugs must be transported from the portal of entry on the body through a variety of biological interfaces to reach the desired receptor site. During this transport, the drug can undergo severe biochemical degradation and, thereby, produce a delivery pattern at the receptor site that differs markedly from the pattern of drug release into the system. The process of molecular diffusion through polymers and synthetic membranes has been used as an effective and reliable means of attaining transdermal controlled release of drugs and pharmacologically active agents.

1.3 Transdermal delivery of drugs- the changing scenario:

In the past twenty four years, transdermal drug delivery has moved from clinical reality being with the first scopolamine patches approved in 1979, to the point where transdermal delivery represents a viable way of delivering a number of drugs with the potential, as research is pursued along many lines, to delivery many more. Some of the

earliest contributions related to transdermal delivery involved understanding the principal permeation barriers in the skin. As early as 1924, Rein hypothesized that the principal resistance to transdermal transport was in a layer of cells joining the stratum corneum to the epidermis. Blank subsequently supported the fact, by doing stripping experiments in which he removed the stratum corneum from the skin surface and showed that the rate of water loss from skin increased dramatically once the last cellular layer of the stratum corneum was eliminated. Scheupin's work established the transdermal penetration was limited by the stratum corneum itself; he showed that molecular impermeability was due to a passive process. The history of transdermal drug delivery is shown in table 1.1 [4].

Table 1.1: Events of the changing scenario of transdermal drug delivery technology:

1900	Iontophoresis, demonstration of enhanced skin transport.
1954	Sonophoresis, demonstration of enhanced skin transport.
1976	Micro needles, patent issued for transdermal delivery phoresor iontophoresis device. FDA approved as a device.
1979	Transderm scop (Scopolamine) patch, FDA approved for motion sickness.
1981	Transdermal-Nitro-Dur and Nitro disc (nitroglycerin) patches, FDA approved for angina.
1983	CF-Indicator (pilocarpine) iontophoresis device, FDA approved for cystic fibrosis diagnosis.
1984	Duragesic (fentenyl) patch, FDA approved for analgesia.
1986	Estraderm (17 β- oestradiol) patch, FDA approved for hypertension.
1990	Catapres –TTS (clonidine) patch, FDA approved for hypertension
1991-92	Nicotine patches introduced by four pharmaceutical companies
1991-95	Low frequency sonophoresis, demonstration of transdermal protein delivery.
1993	Skin electroporation, demonstration of enhanced skin transport Testoderm (tersosterone) patch, FDA approval for hypogonadism.
1995	Iontocaine (epinephrine/lidocaine) iontophoresis patch, FDA approved for hormone replacement microneedles demonstration of enhanced skin transport.
1998	Combpatch (oestradiol/norethindrone) patch, FDA approved for hormone replacement microneedls demonstration of enhanced skin transport.
1999	Lidoderm (lidocaine) patch, FDA approval for post-herpatic neuralgia.
2001	Ortho-Evra (ethinyl oestradiol, norlgestromin), FDA approval for glucose monitoring
2003	Oxytrol (oxybutynin) patch, FDA approval for overactive bladder thermal poration, demonstration of enhanced skin transport

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 head will be cured at once, as through it had never ached". Today transdermal drug delivery 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 [5].

The factors influencing the suitability of a drug for TDD are as follows:

- Potency of the drug-- the daily systemic dose should be ≤ 20 mg.
- Molecular size-- the drug should have a MW of < 500 Daltons.
- Lipophilicity-- the logP should be within the range of 1-3.
- Melting point-- should be $< 200°C$.
- Hydrogen bonding groups-- should be ≤ 2.
- Irritation-- the drug should not be irritant directly to the skin.
- Immunogenicity-- the drug should not stimulate an immune reaction in the skin [6].

1.3.1 Transdermal patches as drug delivery device:

The simply designed transdermal patch has undergone a dramatic transformation over the past decade. In its strictest sense, 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 an enhancer.

1.3.1.1 Humble beginnings:

The first transdermal systems were simply pieces of plastic dipped into a drug that was dissolved in alcohol [7]. 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.

The next generation - still in use - 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 re-applied more frequently. Basically, the patch would not stick, as it would be primarily made up of the drug.

1.3.1.2 Next generation patches:

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 time the delivery and create bolus dosing.

1.3.1.3 Nanotechnology gaining hold:

Another enhancer that is gaining advancement is microneedles. Why should a needle that is a few inches long are used to deliver a drug that is only a few atoms large? This technology combines the advantage of a needle and the transdermal patch. The devices are dime-sized pieces of polymer with hundreds of hollow microneedles between 100 and 1,000 micrometers long. These small needles penetrate the top layers of skin and allow the drug to pass through with ease.

This technology can be combined with an electronically controlled micropump that delivers the drug at specific times or upon demand. These devices allow the patient or physician to control the time and dose of the drug being delivered. These devices have the potential to place drugs precisely into the area where special immune cells reside, making these drugs capable of modulating the immune system, with relative ease.

Alza Corporation is using a slightly different variation on the use of needles. The company has developed the patented Macroflux transdermal technology that uses microprojections to create superficial pathways through the dead skin barrier. The tips of the projections contain active drug - a quick bolus. Interestingly, the Alza Web site

displays a study where human growth hormone, a rather large protein, was able to reach therapeutic levels hours after the application of the patch.

1.3.1.4 Pain relief:

Pain relief routinely benefits from transdermal patch technology. We are aware of the Duragesic patch. There are several others now on the market. One is Lidoderm, a patch containing lidocaine 5 %, which is used for post herpetic neuralgia. Other exciting advancements in pain control include the E-Trans fentanyl HCl patch. This credit card-size patch is an active delivery device that has a self-contained battery that delivers pulses of fentanyl HCl, a strong narcotic. This mimics the use of intravenous self-controlled analgesic systems that are very expensive, cumbersome, and require considerable nursing care. Finally, SonoPrep offers a topical anesthetic system with an ultrasound enhancer. This system uses a small ultrasound generator to transport 4 % lidocaine hydrochloride into the skin in an area just big enough to place a catheter into a vein or artery. It anesthetizes the area in less than a minute and can allow for prolonged application for several hours.

These advances will revolutionize the delivery of many drugs, enhancing the application of nanotechnology and giving new options to patients who require biologic drugs. Now polypeptides and even proteins are not need to be injected or infused. These advances will soon fuel Tomorrow's Medicine!

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a time released dose of medication through the skin and into the blood stream. Transdermal patches are used to deliver a wide variety of pharmaceuticals. The first commercially available prescription patch was approved by the U.S. Food and Drug Administration in December 1979, which administered scopolamine for motion sickness. The most well-known skin patch now a days is the nicotine patch which releases nicotine to help quitting the habit of tobacco smoking. Other skin patches administer estrogen for menopause and to prevent osteoporosis after menopause, nitroglycerin for angina, and lidocaine to relieve the pain of shingles (herpes zoster). Recent developments expanded their use to the delivery of hormonal contraceptives, anti-depressants and even pain killers. Some pharmaceuticals must be combined with substances, such as alcohol, that increase

their ability to penetrate the skin in order to be used in a transdermal patch. Molecules of insulin and many other pharmaceuticals, however, are too large to pass through the skin.

In 2005, the Food and Drug Administration, USA announced that they are investigating reports of death and other serious adverse events related to narcotic overdose in patients using Duragesic, the fentanyl transdermal patch for pain control. The Duragesic product label was subsequently updated to add safety information in June 2005.

1.3.2 Skin as the site for transdermal drug delivery:

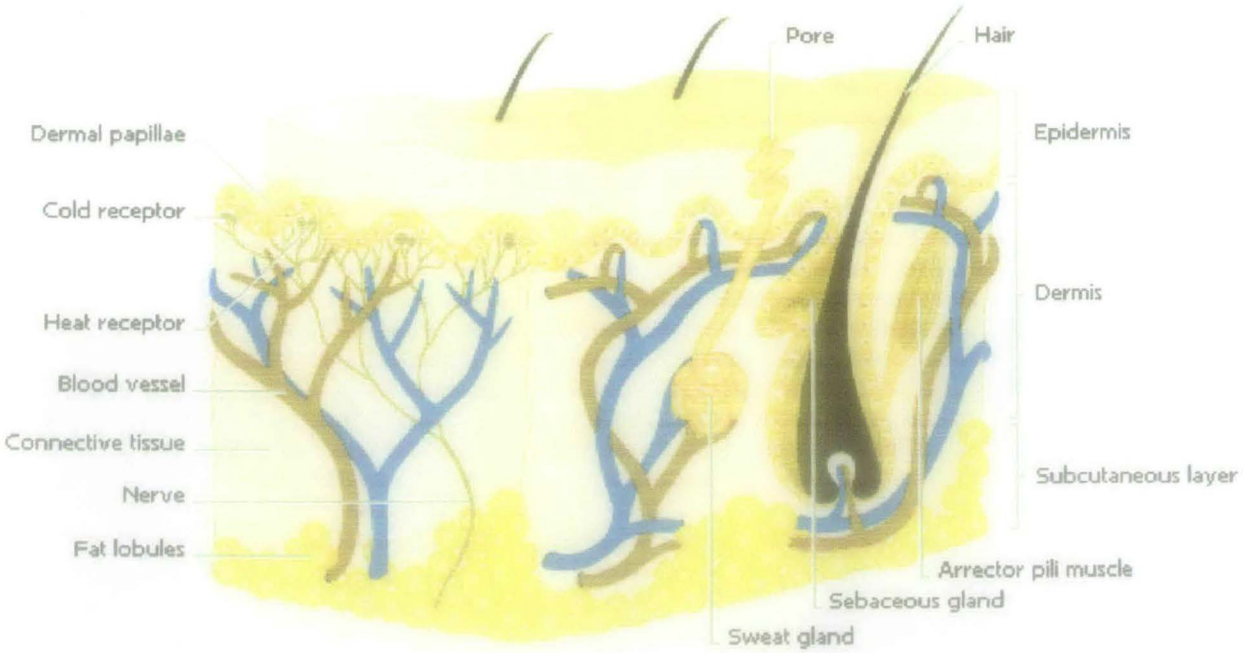
The skin of an average adult covers a surface area of approximately 2 sq.m and receives about one-third of the blood circulating through the body. It is one of the most readily accessible organs of the human body with a thickness of only few millimeters (2.97 ± 0.28 mm). For understanding the concept of transdermal drug delivery system, it is important to review the structural and biochemical features of human skin and those characteristics which contribute to the barrier function and the rate of drug access into the body via skin.

1.3.2.1 Skin anatomy:

The skin is one of the most extensive organs of the human body. It has varied functions and properties with a thickness of only a millimeter. The skin separates the underlying blood circulation network from the outside environment, serves as a barrier agent of physical, chemical and microbial attacks, acts as a thermostat in maintaining body temperature, protects from harmful UV rays of the sun and plays a role in the regulation of blood pressure.

Anatomically, the skin has many histological layers but in general, it is described in terms of three major tissue layers: the epidermis, the dermis and hypodermis [8]. The epidermis results from an active epithelial basal cell population and is approximately 150 micrometer thick. It is the outmost layer of the skin and the process of differentiation results in migration of cells from the basal layer towards the skin surface. The end result of this process is the formation of a thin, stratified and extremely resilient layer (the stratum corneum) at the skin surface. Below this layer are the other layers of the epidermis - the stratum lucidum, stratumgranulosum, stratum spinosum and germinativum. Together, these other layers constitute the viable epidermis.

The human skin surface is known to contain on an average 10-70 hair follicles and 200-300 sweat ducts on every square centimeter of the skin area. These skin appendages occupy only 0.1 % of the total skin surface. Even though foreign agents specially water soluble ones, may be able to penetrate the skin via skin appendages faster than through the intact area of the stratum corneum, this transappendageal route has provided limited contribution to overall transdermal kinetic profile. Therefore the transdermal permeation of most neutral molecules at steady state can be considered as, primarily, a process of passive diffusion through the intact stratum corneum in the interfollicular region. So for fundamental understanding of transdermal drug infusion the organization of skin can be represented by a simplified multilayer model as shown in figure 1.2.



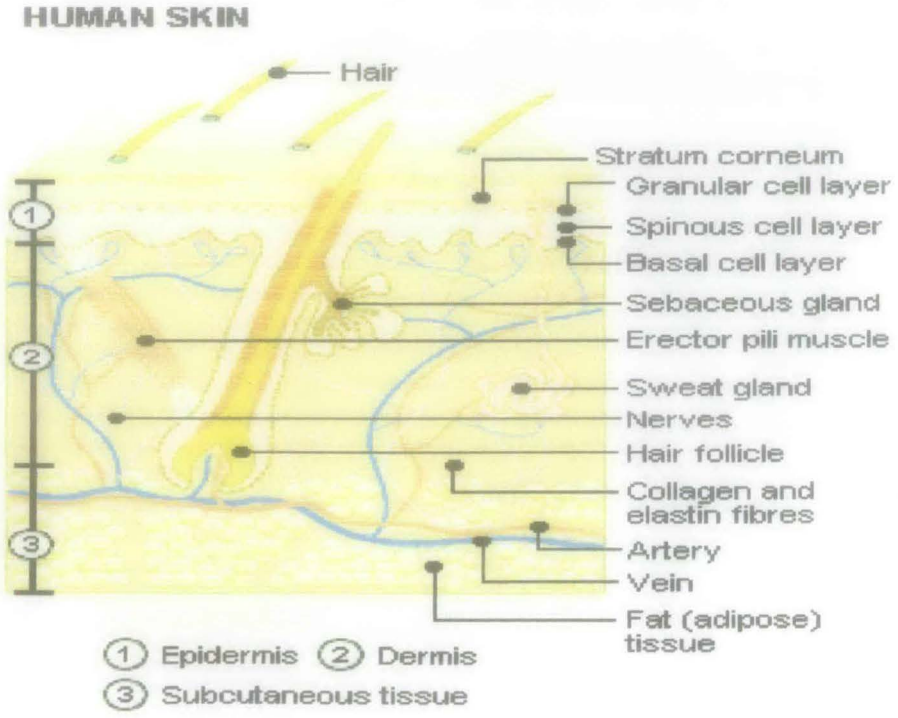


Figure 1.2: Cross sectional view of human skin showing various skin tissue layers and appendages:

The stratum corneum or the horny layer is the rate limiting barrier that restricts the inward and outward movement of chemical substances. Over most of the body, the stratum corneum is composed of 15-25 layers of acutely flattened, metabolically inactive, somewhat polygonal cells having a dry weight density of 1.3 - 1.4 g/cm^3. The thickness of individual cell layers varies from 0.2 micrometer to 0.5 micrometer depending on their location. The interior of these cells is crisscrossed with densely packed bundles of keratin fibers. Due to this, the dry composition of the horny layer is composed of 75-85 % protein, most of which is the intracellular keratin and a part being associated with a network of cell membranes. The bulk of the remainder of the substances of the stratum corneum is a complicated mixture of lipids which lies between the cells. It appears to be organized into bi-layers. The stratum corneum thus has two distinct chemical regions, the mass of intracellular protein and the intercellular lipoidal medium. These phases are isolated from one another by cell membranes which are themselves knit together by desmosomes adding a tough in restructure to the horny mass.

The epidermis rests on the much thicker (2000 micrometer) dermis. The dermis essentially consists of about 80 % of protein (collagen fibers) in a matrix of muco-polysaccharide "ground substance". A rich bed of capillaries is encountered 20 micrometer or so into the dermal field. Also contained within the dermis are lymphatic, nerves and the epidermal appendages such as hair follicles, sebaceous glands and sweat glands. Excepting the soles of the feet, the palms of the hand, red portion of the lips and select portions of the sex organs, the entire skin surface contains hair follicles. Each hair follicle is associated with one or more sebaceous glands which are out growths of epithelial cells. The duct of the sebaceous gland is filled with a soft, slowly extruded lipoidal medium-sebum. About 1/1000 of the total skin surface is occupied by hair follicles. The sweat glands are divided into the eccrine and apocrine types and are widely distributed over the surfaces of the body. Eccrine glands are particularly concentrated in palms and soles (400 glands/ cm^2). The apocrine glands are found around nipples. These are coiled tubular glands, about ten times larger than eccrine glands and extend entirely through the dermis and well into the subcutaneous layer. The sweat glands serve to control body heat by secretion of a dilute salt solution.

1.3.2.2 Lipids contributing the barrier function of the skin:

One major element underlying the impermeability of skin is the hydrophobic nature of the stratum corneum. Major changes in the lipid composition of the epidermis occur as cells move from the basal layer to horny layer. There is a shift from polar lipids to neutral lipids and almost complete loss of phospholipids.

1.3.2.3 Function of the skin:

1. To contain body fluids and tissues - the mechanical function.
2. To protect from potentially harmful external stimuli - the protective or barrier function from
   a) Microorganism; b) chemicals; c) radiation; d) heat; e) electrical barrier; f) mechanical shock
3. To receive external stimuli, i.e., to mediate sensation: a) pressure; b) pain; c) heat.
4. To regulate body temperature.
5. To synthesize and to metabolize compounds.
6. To dispose of chemical waste (glandular secretion).
7. To attract the opposite sex (apocrine secretions are evolutionarily disfunction in this role).
8. To provide identification by skin variation.

Like other tissues of body, the skin has two metabolic requirements, small molecular weight building blocks and chemical energy. Dissimilarities peculiar to the skin are discussed here, as it might affect transdermal drug delivery.

1.3.2.4 Dermis:

The dermis is the largest component of the skin and gives the mechanical strength to the skin. The dermis is arbitrarily divided into two parts: the upper, pappilary, and the lower, reticular [9]. Protein synthesis (from amino acid precursors) is a key factor in dermal metabolism. Fibroblasts produce and deposit extracellularly, huge quantities of collagen and elestin. This becomes important in repair/ turnover of dermal proteins altered by environmental sunlight. Extensive protein synthesis also occurs in hair follicles where hairs, consisting of approximately 95 % protein originate.

The sebaceous glands produce large quantities of lipid (from the two carbon precursor acetate). The energy divided from the intracellular aerobic carbohydrate (glucose) metabolism is used for cellular synthetic processes.

1.3.2.5 Epidermis:

The source of energy for the lower portion of the epidermis is also glucose and the end product of metabolism, lactic acid accumulates in skin, which results in a drop in tissue pH from the usual 7 to less than 6. The cells rely primarily on fatty acids (lipids) for cellular functions. These fatty acids are derived from the degradation of phospholipids from membranes. The energy derived is used in synthesis of the proteins and lipids for construction of stratum corneum.

During differentiation from basal cells to stratum corneum by degradation of the existing cellular components, the entire cellular make up changes. Specialized cellular organelles called lysosomes contain a host of lytic enzymes which they release for intracellular lyses. The epidermis is reservoir of such lytic enzymes. Many of these enzymes are inactivated in upper granular layer; however, many also survive into the stratum corneum. The stratum corneum also has proteolytic enzymes involved in this desquamation.

1.3.2.6 Skin surface:

The skin surface has a population of micro-organisms. They can contribute to the skin enzymology. Their diversity and abundance can vary considerably among individuals and body sites. They can also effect skin surface lipid composition via hydrolysis of secreted sebum.

1.3.3 Percutaneous absorption:

Percutaneous absorption involves passive diffusion of substances through the skin. The mechanism of permeation can involve passage through the epidermis itself (transdermal absorption) or diffusion through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands (transfollicular or shunt pathway absorption).

Routes of penetration:

The drug or diffusant has three potential routes for entry into the subepidermal tissues

1. Through the hair follicles with their associated sebaceous glands.
2. Via sweat glands.
3. Across the continuous stratum corneum between these appendages.

Penetration through the hair follicles and sweat glands can be grouped as appendageal route and penetration across stratum corneum can be further classified as transcellular and intercellular routes.

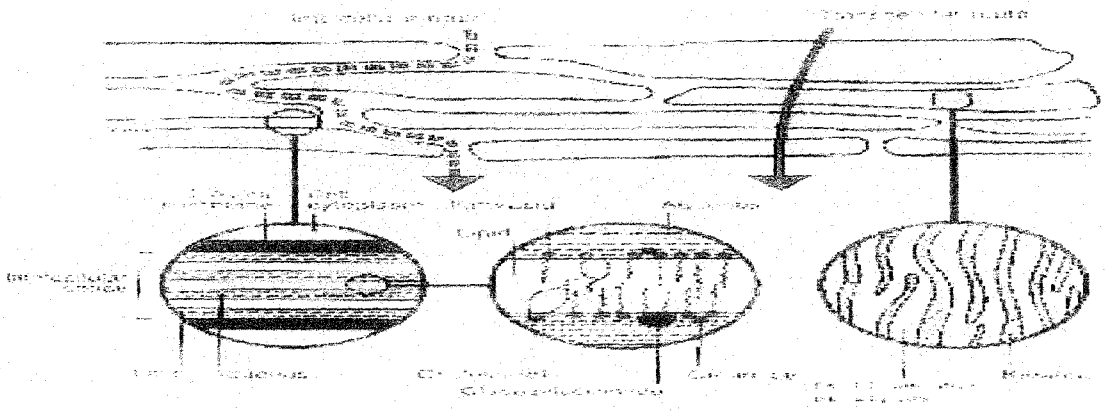


Figure 1.3: Diagrammatic representation of transepidermal routes of penetration through skin:

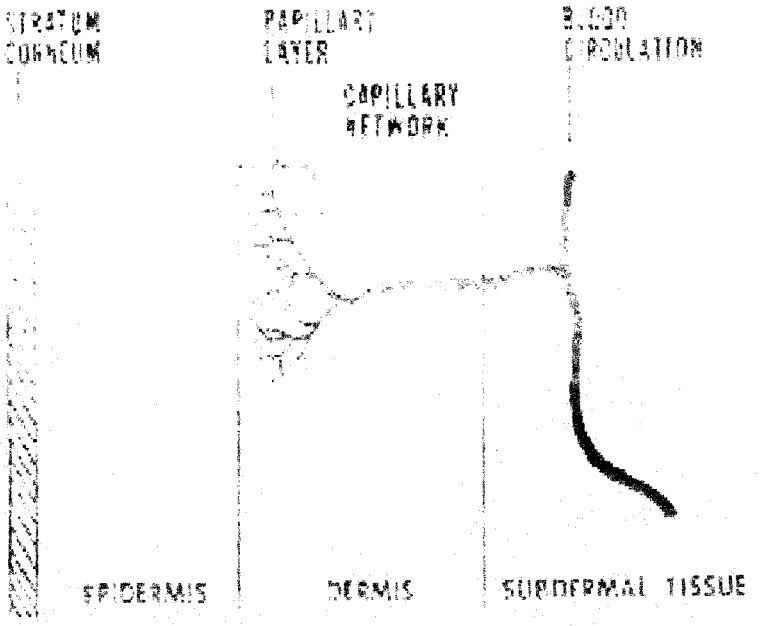


Figure 1.4: Simplified model of human skin for mechanistic analysis of skin permeation:

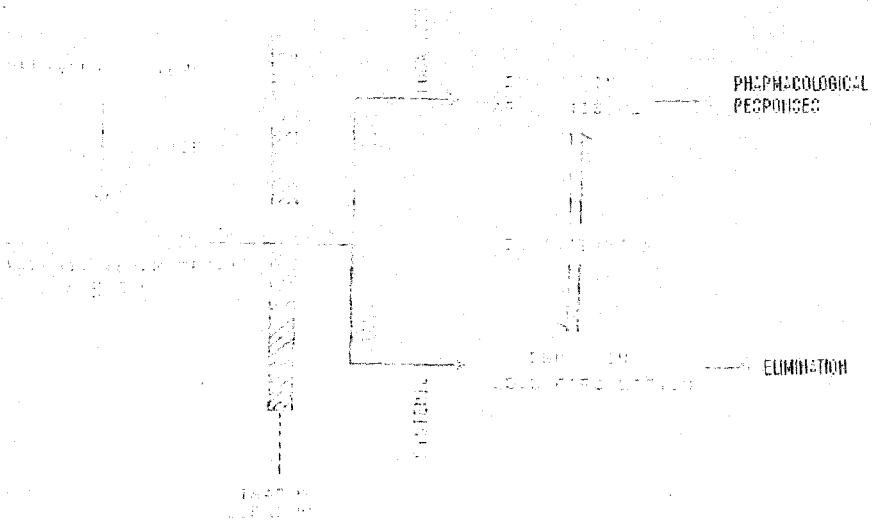


Figure 1.5: Percutaneous absorption of drug for localized therapeutic actions in the skin tissues or for systemic medication in the tissues remote from the site of topical drug application:

1.3.3.1 Factors affecting transdermal permeability:

Transport of drug through skin is influenced by many factors, among which are the nature of the drug itself, the nature of the vehicle, the condition of the skin, and the presence of moisture. The principal factors influencing and causing difference in transdermal permeability of the stratum corneum can be classified as follows.

- Physicochemical properties of the penetrant molecule.
- Physicochemical properties of drug delivery system.
- Physiological and pathological conditions of the skin.

Physicochemical properties of penetrant molecules:

The permeation can be possible only if the drug possesses certain physicochemical properties. The physicochemical properties of the drug are the most important criteria for the judicious selection and the use of drug for effective transdermal permeation. The important physicochemical properties that primarily effect its diffusion through the device and skin include molecular weight, solubility, melting point, chemical functionality etc. The salient approaches governing the physicochemical properties of drug which influence the transdermal permeability include:

- Diffusion of drug across the stratum corneum.
- Drug partitioning from the stratum corneum into the viable epidermis.
- Drug transport within the delivery system to the device-skin surface interface.
- Transport of the drug through the viable tissue.
- Drug uptake by the cutaneous microcapillary net work and subsequent systemic distribution.

Diffusion:

The transport characteristics of the drug are determined primarily by its size and by its level of interaction with the media through which diffusion is taking place, i.e. delivery system, stratum corneum, viable epidermis. Most drugs in current use have molecular weight of less than 1000 dalton. Beyond this magnitude, organic molecules tend to fall into categories such as polymer or peptides. The drugs having molecular weights less than 300 dalton have been widely accepted for transdermal patches for reasons of better

diffusion characteristics. However, drugs having molecular weight of more than 300 are also delivered through other suitable technique like iontophoresis.

For the small species (< 1000 dalton) the effect of size on diffusion in liquid may be viewed in terms of the Stokes-Einstein equation, that is $D = C.M^{-1/3}$

Where, M = molecular weight, C = concentration, D = diffusion coefficient.

Although this is an ideal equation which makes the assumption that the molecules are spherical, it does provide a reasonable estimate of the molecular size on diffusion. It also implies that the molecular weight plays a significant role in influencing diffusion (D). Similarly, minor changes in chemical functionality, solubility characteristics, melting properties can lead to dramatic alterations in permeation behaviors.

Partition coefficient:

There are two key partitioning processes, between the delivery system and the stratum corneum and between the lipophilic stratum corneum and the much more aqueous in nature viable epidermis. Hence, the partitioning criteria of the drug are of paramount importance. The molecule must favor the stratum corneum over the device and then the relative affinity of the drug from the device to corneum and viable tissue must be reasonably high to ensure adequate input of material in to the systemic circulation. Thus extreme partitioning characteristics are not conducive to successful drug delivery via the skin. The majority of topically partitioning drugs are covalent compounds in nature. Regardless of the type of vehicle used, at some point during the process of transdermal penetration the drug molecules have to dissolve and diffuse within the endogenous hydrated tissue of the stratum corneum.

Drug possessing both water and lipid solubility are favorably absorbed through the skin. A lipid /water partition coefficient of one or greater is generally required for optimal transdermal permeability. The partition coefficient of drug molecule may be altered by chemical modification of its functional groups [10]. This has to be done without affecting the pharmacological activity of the drug. The partition coefficient of a drug molecule may also be altered by varying the vehicle.

pH condition:

The pH condition of the skin surface in the drug delivery systems affects the extent of dissociation of inorganic drug molecules and their transdermal permeability. Application of solutions whose pH values are very high or low can be destructive to the skin. With moderate pH values, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charge or uncharged species and their transdermal permeability. In the studies on ephedrine and scopolamine, it has been demonstrated that the maximum transdermal flux of the drug increases with increasing pH up to approximately 1-2 pH units higher than pk_a values, at which point the drug molecule exist totally as the non-protonated form, further increases in pH have no additional effect on drug permeability. The pH dependence of the transdermal permeability was related to the effect of the solution pH on the concentration of lipophilic, non- ionized species of the drug.

Concentration of penetrant molecules:

As transdermal permeability across the skin takes place mostly by passive diffusion, concentration of penetrant molecule is important. Generally the amount of drug transport across the skin (per unit of skin surface area per unit time interval) is proportional to the delivery device. It was seen that the flux of solute is proportional to the concentration gradient across the entire barrier phase. One requirement for maximal flux in a thermodynamically stable situation is that the donor solution should be saturated. A formulation can optimize the solubility of a drug such as corticosteroid by controlling the solvent composition of the vehicle. At concentrations higher than solubility, excess solid drug functions as a reservoir and helps to maintain a constant drug concentration for a prolonged period of time.

Physicochemical properties of drug delivery systems:

Generally the vehicle of drug delivery system does not increase the rate of penetration of a drug into the skin but serves as carriers for the drug [11].

Release characteristics:

Solubility of the drug in the vehicle determines the release rate. The mechanisms of drug release depend on the following factors.

1. Whether the drug molecules are dissolved or suspended in the delivery system.
2. The interfacial partition coefficient of the drug from the system to the skin tissue.

3. pH of the vehicle.

The pH of the vehicle can influence the rate of release of the drug from the delivery system since the thermodynamic activity of acidic and basic drug is affected by the pH. Thus for acidic drugs, the activity changes rapidly when the pH is greater than the pk_a of the drug species. Similarly the activity for the basic drugs is influenced when pH of the vehicle is lower than the pk_w - pk_b value of the drug.

Composition of drug delivery system:

The composition of the drug delivery system not only affects the rate of drug release, but also the permeability of stratum corneum by means of hydration, mixing with skin lipid, or other sorption promoting effect. Presence of any skin hydrating agent like PEGs alters the skin conditions and render improved permeation of the content of delivery system. The extensive literature studies on the effect of the vehicle and the effect of variation in vehicle composition on the transdermal permeability of topical anti-inflammatory drugs such as corticosteroids, indicates that the transdermal permeability of such drugs increase exponentially as the volume fraction of propylene glycol in the vehicle increases.

Enhancement of transdermal permeation:

Majority of drug will not penetrate the skin at sufficiently higher rates for therapeutic efficacy with the exception of scopolamine and nitroglycerine, which penetrate at optimum levels. In order to allow clinically useful transdermal permeation of most drugs, the penetration can be improved by the addition of a permeation promoter into the drug delivery systems. The low permeability of the skin relative to other biological tissues is well known and it is perhaps the fact that the skin serve as a minor part of entry for drugs. As compared to the oral or gastric mucosa the stratum corneum is compacted and highly keratinized. The lipids and proteins of stratum corneum provide a complex structure that is quite impermeable. An enhancer is compound which alters the skin as a barrier to the flux of a desired permeant.

The ideal penetration enhancers are

1. Surfactants as penetration enhancer.
2. Solvent as penetration enhancer.
3. Binary systems as penetration enhancer and

4. Azone as penetration enhancer.

Physiological and pathological conditions of the skin:

It is axiomatic that skin disorders will affect the nature of the skin barrier and hence will influence transdermal drug delivery. However, there are few physiological factors that can influence a lot the rate of drug delivery through the healthy skin.

Reservoir effect of the horny layer:

The horny layer especially is deep layers can sometimes act as depot and modify the transdermal permeation characteristics of some drugs. The reservoir effect is due to the irreversible binding of a part of the applied drug with the skin. This binding can be reduced by the pretreatment of the skin surface with anionic surfactant.

Lipid film:

The lipid film on the skin surface acts as a protective layer to prevent the removal of moisture from the skin and helps in maintaining the barrier function of stratum corneum. Defating of this film was found to decrease transdermal absorption.

Hydration of stratum corneum:

Hydration of stratum corneum can enhance transdermal permeability, although the degree of penetration enhancement varies from drug to drug. Skin hydration can be achieved simply by covering or occluding the skin with plastic sheet, leading to the accumulation of sweat and condensed water vapors. Increased hydration appears to open up the dense, closely packed cells of the skin and increase its porosity, occlusion also reduces the irreversible binding capacity of stratum corneum.

Temperature:

Temperature is expected to enhance the transdermal delivery of various drugs by increasing skin permeability, body fluid circulation, blood vessel wall permeability, rate limiting membrane permeability, and drug solubility. Diffusion through the skin, as elsewhere, is a temperature dependent process, so raising the skin temperature should add thermodynamic drive [12]. Increased skin permeability of lipophilic drugs results from temperature-induced alteration of the lipid structure, which involves the disordered

arrangement of the lipid bilayer structure and its fluidization. The relationship between blood flow and the transdermal absorption of nitroglycerin has been demonstrated in a study in which nitroglycerin patches applied to an area of the upper arm were heated locally by infrared light for 15 minutes [13].

Humidity:

It is well established that the horny layer of skin becomes dry and relatively inelastic at very low relative humidity. When the ambient humidity is very high, the stratum corneum becomes soft and supple. Protracted exposure to dry air during the cold winter months can produce a "dry skin condition", in which the skin surface is scaly and pruritus. At its worst, dry skin is crisscrossed with deep fissures. Skin in this fissured state is visibly damaged and inflamed and is evidently highly permeable to applied chemicals. Water is the principal plasticizer of the stratum corneum and drying of horny tissue stiffens its keratin by removing moisture from between the strands, thereby increasing strand-to-strand interaction. This stiffening should cause a decrease in the permeability of any substance which preferentially courses through the intracellular keratin regime. Humidity has been directly related to the skin permeability by way of its effects on insensible perspiration.

Age:

The most widely investigated physiological factor affecting transdermal drug permeability is that of skin ageing. There are clear structural and functional alterations that occur to the membrane as it ages. There is substantial clinical evidence that the skin of premature infants is extremely permeable. The moisture content of human skin decreases with age; since transdermal delivery is influenced by tissue hydration, this factor could alter drug permeation [14]. Beyond the skin membrane, there are same age-related alterations that theoretically can affect the amounts of a topically applied drug entering the systemic circulation. Blood flow (dermal clearance of molecules traversing the tissue) tends to decrease with age and this could reduce transdermal drug flux *in vivo*.

Gender:

Though there are stricking differences in the general appearance of skin and the distribution and prominence of hair between post adolescent males and females, for

example, keratinocytes tend to be slightly larger in females (37 to 46 mm) than in males (34 to 44 mm), but there are no reports of significant differences in drug permeation between equivalent sites in the two sexes. The unique quality of skin is that it determines its membrane function more than any other factor as the layers of skin essentially provide protection from water loss, which does not differ between the sexes.

Body site:

It is apparent that skin structure varies to some degree over the human body; the stratum corneum is thicker on the palms of the hands and soles of the feet (i.e., the load-bearing area of the body) than on the lips or eyelids. However, the relative permeability of different skin sites is not simply a function of stratum corneum thicknesses as different permeants exhibit varied ranks orders through different skin sites with similar thicknesses of stratum corneum, and the some areas with different stratum corneum thicknesses provide similar levels of drug absorption. Variation in drug absorption can be seen for site with similar thickness of stratum corneum, and that some areas with different stratum corneum thicknesses provide similar levels of drug abruption [15]. Though site-to-site variation in permeability is complex there are some general trends shown in numerous literature reports on the subjects. It is apparent that genital tissue usually provides most permeable site for transdermal drug delivery. The skin of the head and neck is also relatively permeable compared to other sites of the body such as the arms and legs. Intermediate permeabilities for most drug are found on the trunk of the body. Thus, a generalized rank order of site permebilities is: Genital > head and neck > trunk > arm > leg. Thus there is a clear scientific rationale for selecting the application site based on permeability:

General health of subject:

Many general diseases have their skin manifestation where the changes in the skin, amount of discoloration or altered pigmentation with no physical break-up of exterior structures of the skin, it is possible of that the permeability condition of the skin is little altered. Persons in severe state of malnourishment or even suffering from starvation seen to have skin which meets the minimal barrier function for conservation of body water and heat.

Pathological disorders:

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. Psoriasis is one of the most common skin diseases, though it manifests in various cases. It is a chronic recurring non-infection scaling skin condition characterized by erythematous plaques covered with silvery scales. Erythema as a result of ultraviolet radiation increases absorption, as do mild thermal burns, but burns severe enough to resulting protein denaturation and cellular destruction decreases absorption owing to the formulation of an anatomical barrier. Even mild sun burn and inflamed skin exhibits increased permeability to organic substances. Eczema, from the Greek "to boil over", is a further non- infection eruptive condition, in which blistering occurs. The term eczema has no clear universally accepted definition, and is often included within dermatitis is chronic inflammation of the epidermis usually with a strong genetic predisposition from parents who may have, for example, asthma or allergic rhinitis. Atopic dermatitis may affect 15 % of the infants, with the onset usually occurring before the child's first birth day. 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 up to 10 fold. Intact skin is a highly effective barrier against ingress of microorganisms. However, the tissue also carries microbial flora, including bacteria and yeasts if branched, then infection can result. The damage caused to the skin barrier integrity will vary with severity of the infection. In cases such as necrotizing facilities, it is obvious that the barrier is seriously impaired. With the presence of a hand wart, only a very small fraction of the skin surface is involved, and the effect of hyperkeratinisation on drug flux through the wart site is probably marginal. What is apparent, however, is that in all cases of infection outlined above, the effect on barrier integrity will always diminish its effectiveness. This may be advantageous where topical therapy for the infection is decreased, but barrier of dynamic and will be restored as the condition improves; hence, drug flux across the repairing tissue will be expected to slow.

Cutaneous drug metabolism:

The skin metabolizes steroids, hormones, chemical carcinogens and some drugs. The viable epidermis which contains most of the catabolic enzymes that might render a

drug inactive by metabolism is metabolically more active than dermis. It was reported that more than 95 % of the testosterone absorbed was metabolized as penetrated through the skin.

Factors associated with skin conditioning:

When waters saturates the skin the tissue swells, softens and wrinkles and its permeability increases markedly. Little is known concerning the effect of bathing or other cosmetic practices on the barrier state of the skin. It is known that soap and water scrubbing removes surface grime and the natural sebaceous residues which are leaked out into the skin. Excess exposure to harsh detergent solutions or excessive bathing leave the skin drug and pruitic and in extreme situation highly irritated. Soaps and detergents also denature the proteins of the horny layer. Skin in this state is presumably more permeable than normal skin. The use of bath oil and of lotions and the creams quickly restore the general function for its pliability and to help hold water in the stratum corneum.

Drug metabolism by skin organisms:

In normal skins, microorganisms lie either on the surface or just under the outermost loose layer of stratum corneum, often as micro colonies. These organisms tend to aggregate around hair follicles and sebaceous glands, and many extend deep into the follicular canals, serving as a reservoir from which to replenish the surface flora. With such potentially high numbers of organisms, it is also conceivable that some topically applied drugs may be metabolized prior to penetrating the tissue. The microorganism like staphylococci can hydrolyze a wide range of natural and synthetic lipid and other ester substances demonstrating an apparently widespread activity against simple water soluble esters while showing a more variable effect upon long chain triglycerides.

Skin microorganisms can be shown to carry out biotransformation of therapeutic agents under suitable condition *in vitro*. The ability to undertake similar chemically significant drug modifications *in vitro* however will be a function of the metabolic capacity of the prevalent strains drug microbe contact time and microbial population density. Given a suitable flora and prolong contact, the limiting factor will inevitably be the burden of the microorganism present, under these circumstances any condition which

is likely to reduce the level of the organisms, initial skin cleansing, formulation preservative, intrinsic antimicrobial activity will minimize the degradation risk [16].

Iontophoresis:

Numerous literature reports have revealed successfully enhanced delivery of variety of drugs across biological membranes by means of the technique of iontophoresis. Iontophoresis is a process in which the transport of ions into or through the skin is increased by the application of an external electric field across the human skin. The constant current density used is 0.5 mA/cm^2 at maximum (no unbearable pain or prolonged skin irritation) [17]. Iontophoresis uses the potencial difference between two electrodes to transport solutes. The use of iontophoretic current has been shown to enhance significantly the rate of drug delivery from transdermal device over the corresponding passive transport.

Iontophoresis enhances transdermal drug delivery by three mechanisms:

- The electro repulsion (Migration), which enhances the flux of charged molecules[18].
- The electrometric solvent flow, which enhances the flux of both charged and neutral molecules [19], and
- The increased permeability of skin by the flow of electric current. The applied potential differences across the skin can lead to alterations in the tissue permeability, which nonetheless has no great significance.

Potential difference across the skin between two opposite sign electrodes cause electrorepulsion of ions through the skin. Electrorepulsion has taken place due to the repulsion between the electrode and the drug of the same sign. It is the most important mechanism in the iontophoresis of small drug molecules. The significance of electrorepulsion and electroosmosis depends on the physicochemical and electrical properties of the membrane and of the permeant [20,21]. Electro osmotic flow is bulk fluid flow, which occurs when an electrical field is applied across a charged membrane. Electro osmotic flow takes place always in the same direction as the flow of counter ions (from anode to cathode in the skin) and may either hinder or assist drug transport. The role of electroosmotic flow in the transdermal iontophoretic permeation has been studied extensively. The amount of electro osmotic flow has been predicted by theoretical models. It has been demonstrated that the electro osmotic flow can modulate by the properties of

the permeate. It is generally accepted that the contribution of electro osmotic flux becomes greater, as compared to electrorepulsion, as the molecular size of an ion increases. Lipophilic, cationic drugs, e.g. LHRH-peptides and β-blocking agents can evoke a dramatic effect on permeability properties of human skin and on the extent and direction of electroosmotic flow [22]. These lipophilic cations are able to become strongly associated with the net negative charge on the membrane when iontophoresed at neutral pH 7.4 and essentially, to stop completely the electroosmotic flow by neutralization the charge of the skin membrane. Iontophoresis may provide a safe, economical and convenient way to administer charged or uncharged drug transdemally in a controlled manner. The potent advantage is that, since the rate of delivery is controllable, the patient could titrate himself to a point where pain relief was achieved and maintained without eliciting major systemic side effects.

Prodrug [23]:

For drugs which cannot be administered transdermally at a rate high enough to achieve a therapeutic blood level it is required to involve methods to reduce the skin barrier properties. Prodrugs can be used to enhance the permeation of drug. The prodrugs are pharmacologically inactive drug molecules which require chemical or enzymatic transformation to release the active parent molecule prior to exhibiting their pharmacological activities. The prodrug concept can be applied in transdermal controlled drug delivery by altering skin permeability via modification of physicochemical properties of the drug molecule to enhance its rate of transdermal permeation. Prodrugs of a poorly skin permeable drug may be synthesized to improve percutaneous absorption characteristics. During the course of transdermal permeation, the prodrugs can be transformed, by the drug. In other words, if an active drug has a rather low affinity towards the skin, it will not easily partition into it to any great extent. The partition behavior of such a drug can be improved by simple chemical modification to form a lipophilic prodrug. Upon absorption and penetration through the skin, the prodrug is rapidly metabolized to regenerate the active parent drug. However, high prodrug concentration in the skin may lead to enzyme saturation, which hinders the conversion of a prodrug into an active drug molecule.

functions as a viscid watery regime to most penetrants. It appears that only ions and polar nonelectrolytes found at the hydrophilic extreme and lipophilic nonelectrolytes at the hydrophobic extreme have any real difficulty in passing through the viable field. The epidermal cell membranes are tightly joined and there is little to an intracellular space for ions and polar nonelectrolyte molecules to diffusionally squeeze through. Thus, permeation requires frequent crossings of cell membranes, each crossing being a thermodynamically prohibitive event for such water-soluble species. Extremely lipophilic molecules, on the other hand, are thermodynamically constrained from dissolving in the watery regime of the cell (the cytoplasm). Thus the viable tissue is rate determining when nonpolar compounds are involved.

Passage through the dermal region represents a final hurdle to systemic entry. This is so regardless of whether permeation is transepidermal or by shunt route. Permeation through the dermis is through the interlocking channels of the ground substance. Diffusion through the dermis is facile and without molecular selectivity since gaps between the collagen fibers are far too wide to filter large molecules. Since the viable epidermis and dermis lack major physiochemical distinction, they are generally considered as a single field of diffusion, except when penetrants of extreme polarity are involved, as the epidermis offers measurable resistance to such species.

1.3.3.4 Transfolicular (shunt pathway) absorption:

The skins appendages offer only secondary avenues for permeation, sebaceous and eccrine glands are the only appendages which are seriously considered as shunts bypassing the stratum corneum since these are distributed over the entire body. Though eccrine glands are numerous, their orifices are tiny and add up to a minicule fraction of the body surface. More-over, they are either evacuated or so profusely active that molecule cannot diffuse inwardly against the glands output. For these reasons, they are not considered as a serious route for percutaneous absorption since the opening of the follicular pore, where the hair shaft exist the skin, is relatively large and sebum aids in diffusion through the sebum to the depths of the epidermis, is the envisioned mechanism of permeation by the route. Vasculature sub serving the hair follicle located in the dermis is the likely point of systemic entry.

1.3.3.5 Drug metabolism in skin:

Skin is capable of metabolizing endogenous and exogenous substances. The biotransformation reactions in skin comprise of conjugation, oxidation, reduction and hydrolysis. Many lipophilic drugs are eliminated by biotransformation in the skin. For example cortisol and norepinephrine are biotransformed by oxidation reaction in the skin. Progesterone and esterone are reduced in the skin. When the skin is capable of inactivating the drugs metabolically, the local bioavailability depends on the release rate of drug, other skin conditions and also concentration of the drug in the system and on the enzyme activity of the skin.

1.3.3.6 Clearance by local circulation:

The earliest possible point of entry of drugs and chemicals into the systemic circulation is within the papillary plexus in the upper dermis. The process of percutaneous absorption is generally regarded as ending at this point. However, some molecules by-pass the circulation and diffuse deeper into the dermis.

1.3.4 Kinetics of transdermal permeation [25]:

The mechanism of drug release depends upon whether the drug is dissolved or suspended in the delivery system and on the partition of the drug from the delivery system to the skin. The pH of the vehicle can also affect the release of the drug. For acidic drug, activity changes rapidly when pH is greater than pk_s of the drug. The activity of the basic drug is affected when the pH of the vehicle is lower than the $pk_w - pk_b$ value of the drug. Composition of the drug delivery system may affect the rate of drug release, permeation through stratum corneum by means of hydration, mixing with skin lipid or sorption promotion effects.

A drug administered transdermally partitions on the surface of the skin, with some penetrating the skin and finally being transported away by the circulation system. Once in the blood, the drug molecules are distributed throughout the body or eliminated following the body pharmacokinetics. Since the skin generally serves as a major barrier membrane either physically or enzymatically against the entry of foreign materials including drugs, the drug concentration in the body or plasma following transdermal delivery responds slowly compared to that following oral or intravenous administration.

Knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic systems. Transdermal permeation of a drug involves the following steps.

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

The rate of permeation across the skin (dq/dt) is given by------

$$dq/dt = P_s (C_d - C_r) \text{ .....(1)}$$

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

$$P_s = K_s . D_{ss}/ h_s \text{ ..... (2)}$$

Where, K_s is the partition coefficient for the interfacial partitioning of the penetrant molecules from the a solution medium or a transdermal therapeutic system on to the stratum corneum, D_{ss} is the apparent diffusivity for the steady state diffusion of the penetrant molecules through a thickness of skin tissue and h_s is the overall thickness of skin tissues. The permeability coefficient (P_s) for a skin penetrant can be considered to be constant since K_s, D_{ss} and h_s are essentially constant under a fixed condition.

From equation (1) it is clear that a constant rate of drug permeation can be obtained only when $C_d >> C_r$ i.e., the drug concentration at the surface of the stratum corneum (C_d) is consistently and substantially greater than the drug concentration in the body (C_r). The equation (1) becomes:

$$dq/dt = P_s C_d \text{ ..... (3)}$$

and the rate of skin permeation (dq/dt) is constant through out the course of skin permeation. For keeping C_d constant, the drug should be related from the device at a rate (R_r) that is either constant or greater than the rate of skin uptake (R_a) i.e, $R_r >> R_a$.

Since R_r is greater than R_a, the drug concentration of the skin surface (C_d) 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., $C_d >> C_s$.

Therefore, a maximum rate of skin permeation [(dq/dt)] is obtained and is given the equation:

$$(dq/dt)m = P_s . C_s \quad \ldots\ldots\ldots\ldots\ldots (4)$$

From the above equation, it can be seen that the maximum rate of skin permeation (dq/dt)m 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.

1.3.5 Advantages of transdermal drug delivery system [26]:

The principal advantages of the transdermal patches include avoidance of biochemical degradation of the drug molecule in the gastrointestinal tract, variable gastrointestinal absorption and metabolism in liver, and reduced frequency of drug dosage for short acting drugs. The drug needs to be applied only once in 2 to 3 days or even a week as transdermal patch.

The positive features associated with transdermal therapeutic system, where drugs are being delivered across the skin to achieve systemic effect are summarized as follows:- Transdermal medication does

a.) By-pass hepatic "first pass" and gastro-intestinal incompatibility.

Thus the degradation of drugs in the gastro-intestinal region is prevented and eventually the side effects like gastric irritation and many others due to reaction with the gastric fluid and gastric wall can be avoided.

b.) Reduce side effects due to the optimization of the blood concentration time profile.

As mentioned earlier the side effects are minimized along with the controlled distribution pattern. Plasma concentration reaches a steady state level and thereby fluctuation monitored side effects also can be omitted.

c.) Provide predictable activity over extended period of time.

The maintenance of the steady state concentration in plasma results in the effective use of drugs. The drug concentration within therapeutic index (T.I.) also provide minimum risk factor for a prolong period of time.

d.) Greater patient compliance due to the elimination of multiple dosing schedules.

The transdermal therapeutic system provide continuous drug release into the blood through stratum corneum and that is how steady state level achieved, thus the avoidance of taking twice a day or thrice a day schedule for the patients who are often likely to forget, can be avoided.

e.) Enhance therapeutic efficacy.

Maximum utilization of the drug substance can be achieved by transdermal therapeutic system, as drug concentration in plasma remain within minimum effective concentration (MEC) and maximum safety concentration (MSC) for a extended period of time.

f.) Reduce frequency of administration of dosage forms.

As most of the transdermal therapeutic system serves as a drug delivery system for more than 24 hours, hazards of taking drugs frequently can thus be avoided by replacing conventional dosage form with transdermal therapeutic system.

g.) Minimize inter and intra patient variation.

More or less the structure of skin is quite similar among human, so there is no such constrain in making or using transdermal therapeutic system of very particular in type.

h.) Provide suitability for self-administration.

Patient can administer the drug through transdermal patch by simply sticking the patch on to the skin without undergoing an expert's supervision.

1.3.6 Disadvantages of transdermal drug delivery system:

Though transdermal drug delivery system has number of advantages and also they proved to be a revolutionized concept in the field of novel drug delivery system, they suffer from two distinct disadvantages. These are –

a) Difficulty in permeation through intact human skin.

The structure of Skin renders itself as a semi-permeable membrane through which transportation of drug molecules are really tough and where the molecules are not matching with the specified pore size, it won't allow the drug to pass in.

b) Skin irritation.

Though skin irritation is very subjective, i.e. these symptoms or rather side effect varies in individual to individual.

1.3.7 Classification of transdermal delivery devices:

Different devices are classified depending on the release behavior of the containing drug from the transdermal systems. Broadly these can be summarized as follows [27]:

A) matrix type:
- a) adhesive matrix
- b) hydrophilic matrix
- c) polymeric matrix
- d) microporous matrix

B) reservoir type:
- a) rate limiting membrane
  - single reservoir
  - multi reservoir
- b) without rate limiting membrane
  - hollow reservoir
  - rate limiting adhesive layer
  - microcapsules
  - solubility membrane

C) microsealed drug delivery device:

D) macromolecular type:
- a) ethylene vinyl acetate copolymers
- b) silicone elastomers

E) poroplastic type:

1.3.7.1 Matrix type devices:

The drug in a matrix type system is uniformly dispersed throughout a hydrophilic or a lipophilic polymer matrix, which is then cured into a polymeric disk of predetermined thickness and surface area. The matrix is than glued to an aluminium foil which is sealed to drug impermeable backing through an absorbent pad. Most such system does not have an adhesive overlay but instead possess a peripheral adhesive ring. The matrix should have the following characteristic.

- There should be zero chemical interactions of the matrix polymer with the drug.
- The matrix should not impart excessive resistant to the diffusion of the entrapped drug.
- The matrix should be stable and be able to hold the drug in stable conditions.
- The matrix should be nonirritating to skin and also should adhere well to the skin to provide an appropriate bridging between the skin and the drug.
- Structural integrity should be maintained at higher temperature and humidity.

Commonly employed agents for matrix formulation are polyvinyl pyrrolidone, ethylene vinyl acetate (EVA) copolymers, polyesters, microporous polypropylenes and polysaccharides.

Micro porous matrix type devices:

The patented micro porous rate controlling device consists of a backing material and a drug containing micro porous matrix, which rests on a pressure sensitive adhesive layer. The drug passes through the rate controlling micro porous material.

Hydrophilic matrix devices:

The devices consist of a semisolid state polymeric matrix acting as a reservoir as well as hydrophilic bridge to the skin, which facilitates drug permeation into and through the skin by wetting the skin.

1.3.7.2 Reservoir type devices:

Reservoir type devices with rate limiting membrane:

In the reservoir type devices the drug is stored in a reservoir from which it diffuses through a rate limiting membrane to the site of absorption. One of the advantages of the

system is the near constant release rate of drug from the device. However, rupturing of the rate limiting membrane may also result in a quicker than desired release of drug from the device e.g.

Transderm-Scop (Ciba Pharmaceuticals)

Transderm Nitro (Ciba Pharmaceutical)

Catapress- TTS (Boehringer- Ingelheim)

Estraderm (Ciba Pharmaceuticals).

All the four devices have basic similarities in their design. They all contain backing membrane, reservoir of drug, rate limiting membrane, adhesive, and a peel of release liner.

Multireservoir rate limiting devices:

A characteristic feature of this system is that an enhancer is stored in the compartment separated from the drug reservoir. The system has a conventional impermeable backing of materials followed by a reservoir of a vehicle or an enhancer, a rate limiting membrane and a drug reservoir in the adhesive. In one structural modification of the system, the drug reservoir is accommodated between the rate limiting membrane and the adhesive layer as a separate compartment.

Another modification of such systems is where both the drug and enhancer are dispersed in an adhesive polymer or a polymeric matrix followed by an adhesive overlay. Here the vehicle or enhancer is micro capsulated inside a diffusion controlling membrane and these microcapsules together with the drug are dispersed in an adhesive polymer matrix, which adheres well to the skin.

Devices with rate limiting adhesive layer:

The adhesive diffusion control reservoir type systems differ in the dispersion of drug in the adhesive polymer, which is spread as a thin layer on the impermeable backing. Layers of the rate limiting adhesive polymers without any drug are then spread on top of the reservoir layer. The concept has been utilized in development of transdermal nitroglycerine delivery system.

Micro encapsulated drug reservoir type devices:

When the drug is dispersed as microcapsules throughout the contact adhesive, the rate controlling step in the delivery is the diffusion of the drug through the walls of the microcapsules.

Reservoir devices with solubility membrane:

This type of system has drug dispersed in a polymer matrix as reservoir, which is sandwitched between an impermeable backing and a solubility membrane.

Transdermal devices with hollow reservoir:

The reservoir is in the form of a hollow cylinder having an impermeable backing and a rate limiting membrane that controls the release of drug into the adhesive layer.

1.3.7.3 Micro sealed delivery devices:

The micro sealed transdermal device is the result of the hybridization of the reservoir and matrix type of system and is represented by Nitrodisc. In this system an aqueous suspension of drug is prepared in water soluble polymer. The suspension is then dispersed into a lipid soluble polymer with high speed shear force to form microscopic spherical reservoir with the drug entrapped. Immediately the system is cross linked by the addition of polymeric cross linking agents and a matrix is formed. This matrix is than attached to an aluminium foil plate at the back. The aluminium foil plate is than attached to adhesive polyurethane foam paid which forms the backing. This system has a peripheral adhesive ring.

1.3.7.4 Transdermal delivery of macromolecules:

Typical requirements for transdermal delivery of drugs include low molecular weight (500-10000), low melting characters (150-200°F) aqueous solutions neither too acidic nor basic (between 5 and 9 pH units) and preferably with unit oil/water partition coefficients. Typical macromolecules do not possess these characters and hence are not ideal candidates for transdermal delivery. Advances have been made recently in the fabrication of systems for the rate-controlled delivery of macromolecules (for hormones, enzymes, interferon, bioactive peptides etc.). Both the EVA and silicone elastomers devices involve one common concept i.e. because of the large molecular size of drug the

matrix must have channels to facilitate the release of macromolecules. These devices are used as implants.

Based on the mechanism by which the drug is released, the device can be classified into two categories such as monolithic or matrix system and reservoir or membrane system. The selection of any of these two systems for transdermal drug delivery depends on the major factor i.e. controlling the rate of drug transport and its delivery to the systemic circulation. The total resistance to drug transport from the device across the skin can be considered to be the sum of the diffusional resistances through the device (R_1) and that through the stratum corneum (R_2). It may be assumed that the epidermal resistance is negligible compared with that of the stratum corneum. In general, analogous to the current flow in an electrical circuit having resistances connected in series, the overall rate of drug transport will be inversely proportional to the sum of the two resistances ($R_1 + R_2$). If $R_2 >> R_1$, the overall rate of drug transport will be governed by the rate of drug permeation through the stratum corneum and if $R_1 >> R_2$, the device will control the overall rate.

When the desired rate of drug transport is considerably less than that through the stratum corneum, a reservoir type device control drug delivery is required to attain therapeutic steady-state concentrations of drug in the blood plasma and prevent overdosing. On the other hand, if the drug permeation through stratum corneum is the rate-controlling step, a monolithic or matrix type of delivery system may suffice.

1.3.8 Approaches made for the development of transdermal drug delivery system:

All such transdermal dosage forms have a basic structure comprising of many layers, each having a specific function. Farthest from the skin, when the system is in place, is a backing layer, preventing wetting of the system during use. The second layer is a reservoir that supplies a continuous quantum of drug for the predetermined functional lifetime of the system. Next to the reservoir is the rate control polymeric membrane that regulates the rate of drug during a predetermined time interval.

Four different approaches have been made by modifying the matrix and reservoir type system to obtain effective transdermal drug delivery systems [28].

1.3.8.1 Membrane permeation – controlled systems:

In this type of system, the drug reservoir is totally encapsulated in a shallow compartment molded from a drug-impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be micro porous or non porous e.g. ethylene vinyl acetate (EVA) copolymer, which has a defined drug permeability property. The drug molecules are permitted to release only through the rate-controlling membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid polymer matrix or suspended in an unreachable, viscous liquid medium such as silicone fluid to form a past like suspension. A thin layer of drug compatible, hypoallergenic adhesive polymer e.g. silicone or polyacrylate adhesive may be applied to the external surface of the rate controlling membrane to achieve an intimate contact of the transdermal system and the skin surface.

The constant release rate of the drug is the major advantages of membrane permeation controlled transdermal system. However, a rare risk also exists when an accidental breakage of the rate controlling membrane can result in dose dumping or a rapid release of the entire drug content.

The intrinsic rate of drug release fro this type of drug delivery is defined by

$$dq/dt = \frac{C_R}{1/P_m + 1/P_a} \quad \text{---------- (5)}$$

Where C_R is the drug concentration in the reservoir compartment and P_a and P_m are the permeability coefficient of the adhesive layer and the rate controlling membrane, respectively. For a micro porous membrane, P_m is the sum of permeability coefficient for simultaneous penetration across the pores and the polymeric material. P_m and P_a, respectively, are defined as follows

$$P_m = K_{m/r}. D_m / h_m \text{ ---------- (6)}$$

$$P_a = K_{a/m}. D_a / h_a \text{ ---------- (7)}$$

Where K_{mr} and K_{am} are the partition coefficient for the interfacial partitioning of drug from the reservoir to the membrane and from the membrane to the adhesive layer respectively; D_m and D_a are the diffusion coefficient in the rate controlling membrane and adhesive layer respectively; and h_m and h_a are the thickness of the rate-controlling membrane and adhesive layer, respectively. In the case of micro porous membrane, the porosity and tortuosity of the membrane should be taken into the calculation of the D_m and h_m values.

Substituting equation (2) and (3) for Pm and P_a in equation (1) gives

$$dq/dt = K_{m/r}.\ K_{a/m}.\ D_m.\ D_a / K_{m/r}.\ D_m.\ H_a + K_{a/m}.\ D_a.h_m.\ C_R \text{ ---------- (8)}$$

This defines the intrinsic rate of drug release from a membrane-modulated drug delivery system.

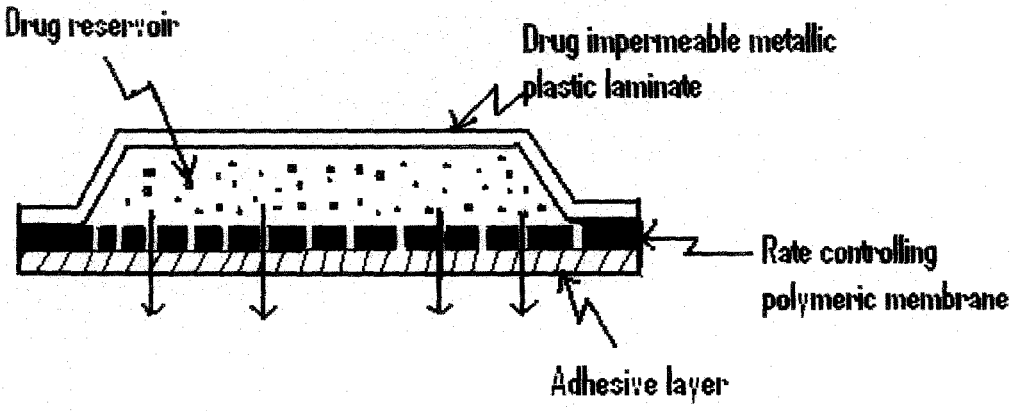


Figure 1.6: Membrane-modulated transdermal drug delivery system:

1.3.8.2 Adhesive dispersion-type systems:

This is a simplified from of the membrane permeation-controlled system. As represented in figure 1.7, the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer e.g. poly (isobutylene) or poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer.

On top of the drug reservoir layer, thin layers of non-medicated, rate-controlling adhesive polymer of a specific permeability and constant thickness are applied to produce an adhesive diffusion-controlled delivery system.

The rate of drug release from this drug reservoir gradient controlled system is expressed as:

$$dq/dt = K_{a/r}.\ D_a / h_a\ (t).\ A\ (h_a) \text{ ---------- (9)}$$

Where, $K_{a/r}$ is the partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer.

In this equation the thickness of the adhesive layer for drug molecules to diffuse through increases with time h_a (t). To compensate for this time-dependent increase in diffusional path due to the depletion of drug dose by release, the drug loading level is also increased with the thickness of diffusional path A (h_a). A constant drug release profile is thus obtained.

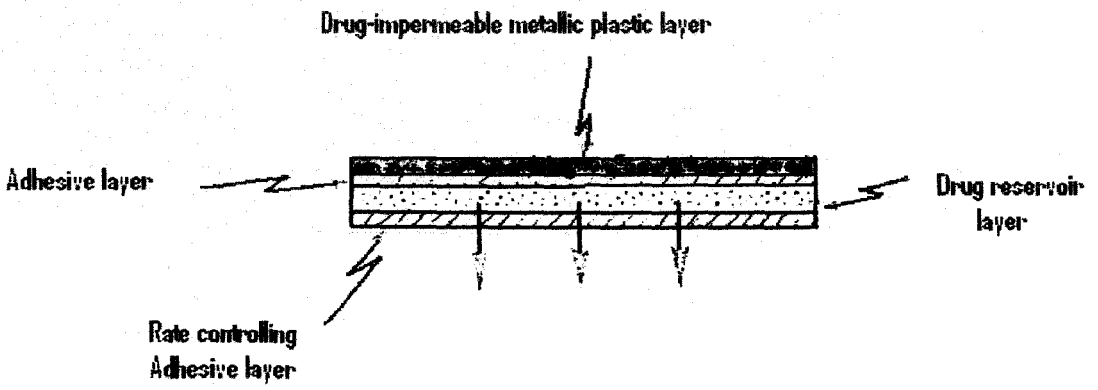


Figure 1.7: Adhesive-dispersion type transdermal drug delivery system:

1.3.8.3 Matrix diffusion-controlled systems:

In this approach, the drug reservoir is prepared by homogeneously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then moulded into a medicated disc with a defined surface area and controlled thickness. The dispersion of drug particles in the polymer matrix can be accomplished by either homogeneously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross-linking of the polymer chains or homogenously blending drug solids with a rubbery polymer at an elevated temperature. The drug reservoir can also be formed by dissolving the drug and polymer in a common solvent followed by solvent evaporation in a mold at an elevated temperature and/or under vacuum. This drug reservoir containing polymer disc is then pasted on to an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing. The adhesive polymer is then spared along the circumference to form a strip of adhesive rim around the medicated disc.

The rate of drug release from this type of system is defined as:

$$dq/dt = [AC_P.D_P/2t\ ]^{1/2} \quad \text{----------} \quad (10)$$

Where, A is the initial drug loading dose dispersed in the polymer matrix and C_P and D_P are the solubility and diffusivity of the drug in the polymer respectively. Since, only the drug species dissolved in the polymer can release, C_P is essentially equal to C_R where C_R is the drug concentration in the reservoir component.

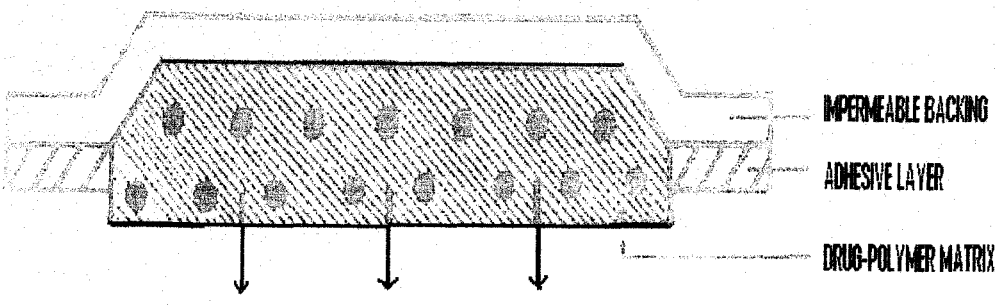


Figure 1.8: Cross sectional view of matrix diffusion controlled transdermal drug delivery system showing major structural components:

The q versus $t^{1/2}$ drug release profile is obtained at steady state and is defined by

$$q/t^{1/2} = [(2A - C_P)\, C_P\, D_P]^{1/2} \text{ ---------- (11)}$$

The advantage of the matrix dispersion type transdermal system is the absence of dose dumping since the polymer cannot rupture.

1.3.8.4 Micro reservoir type or micro sealed dissolution controlled system:

This can be considered a combination of the reservoir and matrix diffusion type drug delivery system. Here the drug reservoir is formed by first suspending the drug solids in an aqueous solution of a water-soluble liquid polymer and then dispersing the drug suspension homogeneously in a lipophilic polymer viz. silicone elastomer by high-energy dispersion technique to form several discrete, unleachable microscopic spheres of drug reservoirs. The quick stabilization of this thermodynamically unstable dispersion is accomplished by immediately cross-linking the polymer chains in-situ that produces a medicated polymer disc with a constant surface area and a fixed thickness. Depending upon the physicochemical property of the drug and the desired rate of drug release, the device can be further coated with a layer of biocompatible polymer to modify the mechanism and rate of drug release. A transdermal therapeutic system is produced by positioning the medicated disc at the centre and surrounding it with an adhesive rim.
The rate of release of drugs from the microreservoir system is defined by

$$dq/dt = D_P.\, D_d.\, m.\, K_P / D_P.h_d + D_d.\, h_p.m.k_p\, [n.S_P\, D_1 S_1\, (1-n)/h_1\, (1/k_1 + 1/k_M)] \text{ -------- (12)}$$

Where m = a/b, a is the ratio of the drug concentration in the bulk of the elution medium over drug solubility in the same medium and b is the ratio of drug concentration at the outer edge of the polymer coating over the drug solubility in the same polymer composition; n is the ratio of drug concentration at the inner edge of the interfacial barrier over drug solubility in the polymer matrix; D_1,D_P and D_d are, respectively, the drug diffusivities in the liquid layer surrounding the drug particles, polymer coating membrane surrounding the polymer matrix and the hydrodynamic diffusion layer surrounding the polymer coating with respective thickness of h_1, h_p; and h_d, k_1, k_m and k_p are the partition coefficient for the interfacial partitioning of the drug from the liquid compartment to the polymer matrix, from the polymer matrix to the polymer coating membrane and from the

polymer coating membrane to the elution solution respectively; $S_1$and S_P are the solubility of the drug in the liquid compartment and in the polymer matrix respectively. The release of drug from this system can follow either a partition control or matrix diffusion-control process depending upon the relative magnitude of S_1 and S_P.

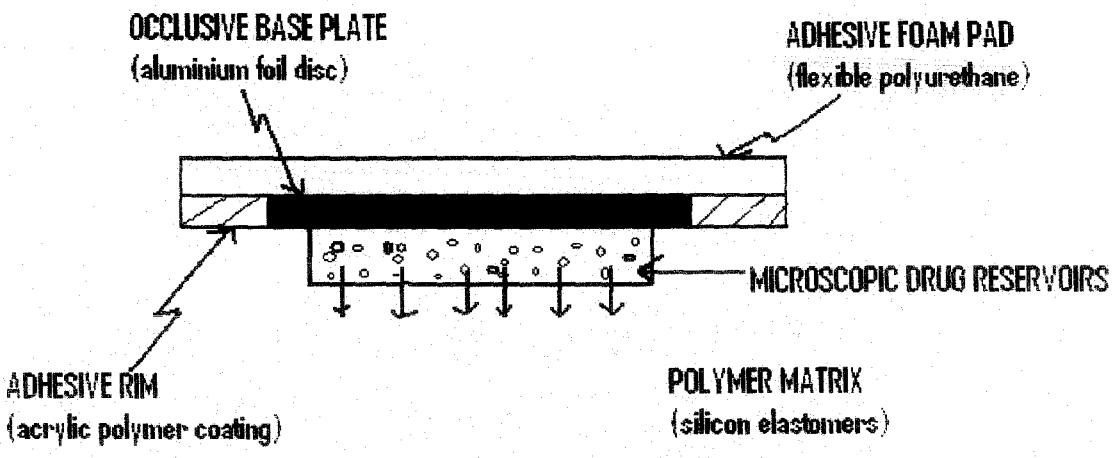


Figure 1.9: Cross sectional view of micro-reservoir type or micro-sealed dissolution controlled system:

1.3.8.5 Other type:

Development of other types of potential drug delivery systems has been complicated and products have started reaching market. These systems are poroplastic membrane and a hydrophilic polymeric reservoir. The poroplastic membrane is an open cell ultramicroporous form of cellulose triacetate. It holds saturated drug solution (water or oil) by capillary action, it can also be described a "molecular sponge". However, the pores are perhaps a million times smaller than those of an ordinary sponge. The molecular weight cut off can be used to estimate a characteristic pore diameter. The pores have reasonable broad size distribution probably; with preponderance below the characteristic diameter of particular importance for transdermal drug delivery through poroplastic membrane is its diffusive permeability which can be varied over broad range.

A new variation on existing polymeric transdermal delivery systems employs hydrophilic gel matrix membrane. The matrix is an "open cell molecular sponge", a plasticizer which contains a drug in a soluble and/or suspended state in a micro space suspended by the polymeric meshwork

of linkages. It contains one or a mixture of hydrogen bonding liquids such as water, glycerin, propylene glycol, polyethylene glycol etc. comprising from 40-70 % patch weight. Gelation agents such as karaya, algin, xanthan, guar, locust bean gum and/or synthetic hydrophilic polymers- polyacrylamide, polyvinyl sulphonates, polyvinyl alcohol, polyacrylic acid, polyvinyl pyrrolidone and other are also used.

Table 1.2: Transdermal delivery systems- recent progress in research and development [29]:

Drug	Indication	Status	Source**
Megestrol acetate	Breast and endometrial carcinoma; weight control	Clinical trial-Phase IV	A
Estradiol	Prostate cancer	Clinical trial-Phase II	A
Fentanyl (in matrix)	Pain	Clinical trial-Phase III	
Nicoderm	Smoking		
Transdermal rotigotine	Idiopthic restless legs syndrome	Clinical trial-Phase III	A
Buprenorphine	Overactive bladder	Clinical trial-Phase IV	A
Morphine	Pain	Clinical trial-Phase I	A
Meglumine antimoniate	Leishmaniasis	Clinical trial-Phase III	A
Transdermal 17-ß-estradiol	Alzheimer's disease	Clinical trial-Phase II	A
Lisuride patch	Parkinson's disease	Clinical trial-Phase II	A
Granisetron	Chemotherapy-induced nausea and vomiting	Clinical trial-Phase III	A
Bupropion	Schizophrenia; smoking	Clinical trial-Phase II	A
Testosterone	Ageing, frail, elderly rehabilitation	Clinical trial-Phase II	A
Buprenorphine	Osteoarthritis	–	B
Human brain natriuretic		Patent	C
Methotrexate	Psoriasis, rheumatoid	Patent	C
N-methulglucamine	Skin disorder		C
Perospirone S	Schizophrenia	Patent	C
Phenserine	Cognitive disorders	Patent	C
Influenza vaccine	Influenza	Patent	C
Tulobuterol	Asthma, chronic bronchitis	Patent	C

**** Till 2006**

(A = www.ClinicalTrials.gov; B = www.centerWatch.com; C =CAPLUS/Medline)

1.3.9 Materials required for the development of transdermal patches [30]:

- Polymer matrix or matrices.
- The drug.
- Permeation enhancers.
- Other excipients.
- Other materials

Polymer matrix:

The polymer controls the release of drug from the devices. The following criteria should be satisfied for a polymer to be used in a transdermal system.

- Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
- The polymer should be stable, non reactive with the drug, easily manufactured and fabricated in to the desired product; and inexpensive.
- The polymer and its degradation product must be nontoxic or non antagonistic to the host.
- The mechanical properties of the polymer should not deteriorate extensively when large amount of active agent are incorporated to it.

Possible useful polymers for transdermal devices are

- Natural polymers:
  Cellulose derivatives, gelatin, shellac, waxes, proteins, gums and their derivatives, natural rubber, starch etc.
- Synthetic elastomers:
  Polybutadiene, hydrin, rubber, polysiloxane, silicone rubber, nitrile, acrylonitrile, butyl rubber, styrene, neoprene etc.
- Synthetic polymers:
  Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc.

Drug:

Several categories of drugs have potential for therapeutic improvement of efficacy via transdermal routes e.g. antihypertensives, steroids, antianginals, antineoplastics and anti-inflammatory agents.

For successfully development of a transdermal drug delivery system, the drug should possess some desirable properties.

Physicochemical properties

- The drug should have a molecular weight less than 1000 daltons.
- The drug should have affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristic are not conductive to successful drug delivery via the skin.
- The drug should have a low melting point.

Biologic properties

- The drug should be potent with a dose of the order of a few mg/day.
- The half-life of the drug should be short.
- The drug must not induce a cutaneous irritant or allergic response.
- Drugs that degrade in G.I. tract or inactivated by hepatic first-pass effect are suitable candidates for transdermal delivery.
- Tolerance to the drug must not develop under the near zero-order release profile of transdermal delivery.
- Drugs which have to be administered for along period of time or which causes adverse effects to non target tissue can also be formulated as transdermal delivery.

Drugs possessing both water and lipid solubility are absorbed through the skin to a greater extent. A lipid/water partition coefficient of one or greater is required for optimal transdermal permeability of the drug. Partition coefficient of the drug can be altered by the chemical modification of the functional groups without affecting the pharmacological activity. The pH conditions of the skin surface and drug delivery system affect the extent of dissociation of ionogenic drug molecules and transdermal permeability. As transdermal permeability across skin takes place mostly by passive diffusion, concentration of penetrant molecule is important.

Permeation enhancers:

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

The flux, J, of the drugs across the skin can be described as,

$$J = D\, dc/dt \text{ ---------- (13)}$$

Where, D is the diffusion coefficient and is a function of size, shape, and flexibility of the diffusion molecules as well as the membrane resistance, C is the concentration of the diffusing species.

Permeation enhancer is hypothesized to affect one or more of skin layers to achieve skin penetration enhancement. A large number of compounds have been investigated for their ability to enhance stratum corneum permeability.

They are classified as

i) Solvents:

Examples include water, methanol and ethanol; alkylmethylsulfoxide, dimethyl sulfoxide, pyrrolidones, propylene glycols, glycerols, isopropyl palmited.

ii) Surfactants:

Anionic surfactants: dioctyl sulphosuccinate, sodium lauryl sulphate, dodecylmethyl sulphoxide etc.

Nonionic surfactants: pluronic F127, pluronic F68 etc.

Bile salts: Sodium taurocholate, deoxycholate, sodium tauroglycocholate.

iii) Miscellaneous chemicals: eucalyptol, di-o-methyl-β-cyclodextrin, soyabean, casein etc.

Presence of enhancers alters the thermodynamic activity of the drug which causes changes in partition tendency. Solvents like water, alcohols, propylene glycol, hydrophilic cosolvents, alkyl methyl sulfoxide, dimethyl acetamide and dimethyl formamide enhance the skin permeability of many drugs.

Permeation pattern of the drugs through skin is altered due to many surfactants. The surfactants reduce the interfacial tension and increase membrane transport. Nonionic surfactants cause less irritation. They increase membrane fluidity, solubilize and extract membrane components.

Other excipients:

Adhesives:

The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive .The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally. It should not be irritant to skin, should be easily removed, and should not leave an unwashable residue on the skin. The adhesive should have physical and chemical compatibility, with drug, excipients and other constituent of the system. It should not effect the permeation of the drug. Some commonly used pressure sensitive adhesives include polyisobutylenes, acrylics and silicons.

Backing membrane:

Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage from the top, and accept printing. It is impermeable substance that protects the product during use on the skin.

Examples of such baking membranes are metallic or plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminium foil), with different alcohols such as polyvinyl alcohol.

Plasticizers:

Plasticizers also play important role in the formulation of transdermal patches. They are considered to be one of the essential components of transdermal patches as they provide stiffness of the formulation.

Commonly used plasticizers are- dibutyl phthalate, propylene glycol, polyethylene glycol (PEG-400), eudraflex.

Other materials:

These include glass molds, aluminum foil or mercury in which the casting solution can be poured to give the transdermal system a desired shape.

1.3.10 Evaluation of transdermal patches:

There are numbers of evaluation parameters for ascertaining reproducible and effective transdermal patches in respect to there fabrication including drug incorporation and release pattern of the containing drug. The *in vitro* model for the study of transdermal drug penetration should have a suitable receptor compartment and a membrane similar to human skin separating the receptor from the donor. The temperature, pH, agitation etc. should be adjusted to simulate the *in vivo* conditions. Franz diffusion cell is commonly used to resemble these criteria. The purpose of study is to predict the delivery of drug to the skin surface, passage of drug through the skin and delivery of the drug from the body to the blood circulation. The transdermal patches are also examined for their strength to withstand the shear stress, drug entrapment and distribution, stability etc.

1.4 Hyper tension – an over view:

Hyper tension is a common disorder, which, if not effectively treated, results in a greatly increased probability of coronary thrombosis, strokes and renal failure. Until about 1950, there was no effective treatment, and the development of antihypertensive drugs, which greatly increase life expectancy, has been a major, but largely unsung, therapeutic success story [31].

1.4.1 What is high blood pressure?

High blood pressure or hypertension means high pressure (tension) in the arteries. The arteries are the vessels that carry blood from the pumping heart to all of the tissues and organs of the body. High blood pressure does not mean excessive emotional tension, although emotional tension and stress can temporarily increase the blood pressure. Normal blood pressure is below 120/80 mmHg; blood pressure between 120/80 and 139/89 is called "pre-hypertension", and a blood pressure of 140/90 or above is considered high blood pressure. The systolic blood pressure, which is the top number, represents the pressure in the arteries as the heart contracts and pumps blood into the arteries. The diastolic pressure, which is the bottom number, represents the pressure in the arteries as the heart relaxes after the contraction. The diastolic pressure, therefore, reflects the minimum pressure to which the arteries are exposed.

An elevation of the systolic and/or diastolic blood pressure increases the risk of developing heart (cardiac) disease, kidney (renal) disease, hardening of the arteries (atherosclerosis or arteriosclerosis), eye damage, and stroke (brain damage). These complications of hypertension are often referred to as end-organ damage because damage to these organs is the end result of chronic (long duration) high blood pressure. Accordingly, the diagnosis of high blood pressure in an individual is important so that efforts can be made to normalize the blood pressure and, thereby, prevent the complications. Since hypertension affects approximately 1 in 4 adults in the United States, it is clearly a major public health problem.

Whereas it was previously thought that diastolic blood pressure elevations were a more important risk factor than systolic elevations, it is now known that for individuals older than 50 years of age systolic hypertension represents a greater risk.

There are a few recognizable and surgical treatable cause of hyper tension, such as phaeochroocytoma ,steroid-secreting tumours of the adrenal cortex, renal artery stenosis and so on, but the great majority of cases involve no obvious causative factor, and are grouped as essential hypertension (so called because was originally thought that the raised blood pressure was essential to maintain adequate tissue perfusion). The pathophysiology is intimately related to the kidneys (as demonstrated by transplantation experiments in which kidneys are transplanted from or to animals with genetic hypertension, or to humans requiring renal transplants therapeutically: hypertension "goes with" the kidney from a hypertensive donor and vice versa) and leads to narrowing of the lumen of systemic arterioles.

1.4.1.1 Causes of high blood pressure:

Two forms of high blood pressure have been described- essential (or primary) hypertension and secondary hypertension. Essential hypertension is a far more common condition and accounts for 95 % of hypertension. The cause of essential hypertension is multifactorial, that is, there are several factors whose combined effects produce hypertension. In secondary hypertension, which accounts for 5 % of hypertension, the high blood pressure is secondary to (caused by) a specific abnormality in one of the organs or systems of the body.

Essential hypertension affects approximately 75 million Americans, yet its basic causes or underlying defects are not always known. Nevertheless, certain associations have been recognized in people with essential hypertension. For example, essential hypertension develops only in groups or societies that have a fairly high intake of salt, exceeding 5.8 grams daily. In fact, salt intake may be a particularly important factor in relation to essential hypertension in several situations. Thus, excess salt may be involved in the hypertension that is associated with advancing age, African American background, obesity, hereditary (genetic) susceptibility, and kidney failure (renal insufficiency).

Genetic factors are thought to play a prominent role in the development of essential hypertension. However, the genes for hypertension have not yet been identified. (Genes are tiny portions of chromosomes that produce the proteins that determine the characteristics of individuals.) The current research in this area is focused on the genetic factors that affect the renin-angiotensin-aldosterone system. This system helps to regulate blood pressure by controlling salt balance and the tone (state of elasticity) of the arteries.

Approximately 30 % of cases of essential hypertension are attributable to genetic factors. For example, in the United States, the incidence of high blood pressure is greater among African Americans than among Caucasians or Asians. Also, in individuals who have one or two parents with hypertension, high blood pressure is twice as common as in the general population. Rarely, certain unusual genetic disorders affecting the hormones of the adrenal glands may lead to hypertension. (These identified genetic disorders are actually considered secondary hypertension).

The vast majority of patients with essential hypertension have in common a particular abnormality of the arteries. That is, they have an increased resistance (stiffness or lack of elasticity) in the tiny arteries that are most distant from the heart (peripheral arteries or arterioles). The arterioles supply oxygen-containing blood and nutrients to all of the tissues of the body. The arterioles are connected by capillaries in the tissues to the venous system (or the veins), which returns the blood to the heart and lungs. Just what makes the peripheral arteries become stiff is not known. Yet, this increased peripheral arteriolar stiffness is present in those individuals whose essential hypertension is associated with genetic factors, obesity, lack of exercise, overuse of salt, and aging. Inflammation also may play a role in hypertension since a prediator of the development of

hypertension is the presence of an elevated carbon reactive protein level (a blood test marker of inflammation) in some individuals [32,33].

Goals of treatment of high blood pressure:

High blood pressure usually exists for many years before its complications develop. The idea, therefore, is to treat hypertension early, before it damages critical organs in the body. Accordingly, increased public awareness and screening programs to detect early, uncomplicated hypertension are the keys to successful treatment. The point is that by treating high blood pressure successfully early enough, one can significantly decrease the risk of stroke, heart attack, and kidney failure.

The goal for patients with combined systolic and diastolic hypertension is to attain a blood pressure of 140/85 mmHg. Bringing the blood pressure down even lower, as mentioned earlier, may be desirable in African American patients, and patients with diabetes or chronic kidney disease. Although life style changes in pre-hypertensive patients is appropriate, it is not well established that treatment with medication of patients with pre-hypertension is beneficial.

1.4.1.2 Starting treatment for high blood pressure:

Blood pressure that is persistently higher than 140/ 90 mmHg usually is treated with lifestyle modifications and medication. If the diastolic pressure remains at the border line level (usually under 90 mmHg, yet persistently above 85), however, more aggressive treatment also can be started in this circumstances. These circumstances include borderline diastolic pressures in association with end-organ damage, systolic hypertension, or factors that increase the risk of cardiovascular disease, such as age over 65 years, African American decent, smoking, hyperlipemia (elevated blood fats), or diabetes.

Any one of the several classes of medications may be started, except the alpha-blocker medications. The alpha-blockers are used only in combination with another anti-hypertensive medication in specific medical situations. In some particular situations, certain classes of anti-hypertensive drugs are preferable to others as the first line (choice) drugs. For example, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blocking (ARB) drugs are the drugs of choice in patients with heart failure, chronic kidney failure (in diabetics or non-diabetics), or heart attack (myocardial

infarction) that weakens the heart muscle (systolic dysfunction). Also, beta-blockers are sometimes the preferred treatment in hypertensive patients with a resting tachycardia (racing heart beat when resting) or an acute (rapid onset, current) heart attack.

Furthermore, patients with hypertension may sometimes have a co-existing, second medical condition. In such cases, a particular class of anti-hypertensive medication or combination of drugs may be chosen as the first line (initial) approach. The idea in these cases is to control the hypertension while also benefiting the second condition. For example, beta-blockers may treat chronic anxiety or migraine headache as well as the hypertension. Also, the combination of an ACE inhibitor and an ARB drug can be used to treat certain diseases of the heart muscle (called cardiomyopathies) and certain kidney diseases where reduction in proteinuria would be beneficial.

In some other situations, certain classes of anti-hypertensive medications should not be used (are contraindicated). Dihydropyridine calcium channel blockers used alone may cause problems for patients with chronic renal disease by tending to increase proteinuria. However, an ACE inhibitor will blunt this effect. Furthermore, the non-dihydropyridine type of calcium channel blockers should not be used in patients with heart failure or certain abnormal heart rates or rhythms (arrhythmias). On the other hand, these drugs may be beneficial in treating certain other arrhythmias. Also, some drugs, such as minoxidil, since it is so powerful, usually are relegated to second or third line choices for treatment. Clonidine is an excellent drug but has side effects such as fatigue, sleepiness, and dry month that make it a second or third line choice. That is, it is used only after all of the first and second line drugs have been tried without success. Finally, the section 1.4.1.5 below describes the anti-hypertensive drugs that are appropriate or inappropriate for use in pregnant women.

1.4.1.3 Treatment with combinations of drugs for high blood pressure:

The use of combination drug therapy for hypertension is not uncommon. At times, using smaller amounts of one or more agents in combination can minimize side effects while maximizing the anti-hypertensive effect. For example, diuretics, which also can be used alone, are more often used in a low dose in combination with another class of anti-hypertensive medications. In this way, the diuretic has fewer side effects while it improves the blood pressure-lowering effect of the other drug. Diuretics also are added to other anti-

hypertensive medications when a patient with hypertension also has fluid retention and swelling (edema).

The ACE inhibitors or angiotensin receptor blockers may be useful in combination with most other anti-hypertensive medications. ACE inhibitors and angiotensin receptor blockers have additive effects in treating patients with cardiomyopathies and proteinuria. Another useful combination is that of a beta-blocker with an alpha-blocker in patients with high blood pressure and enlargement of the prostate gland in order to treat both conditions simultaneously. Caution is necessary, however, when combining two drugs that both lower the heart rate. For example, adding a beta-blocker to a non-dihydropyridine calcium channel blocker (e.g. diltiazem or verapamil) warrants caution. Patients receiving a combination of these two classes of drugs need to be monitored carefully to avoid an excessively slow heart rate (bradycardia). Combining alpha and beta-blockers may be beneficial for cardiomyopathies and hypertension. Carvedilol is useful for cardiomyopathies and labetalol for hypertension patients.

1.4.1.4 Emergency treatment of high blood pressure:

In a hospital setting, injectable drugs may be used for the emergency treatment of hypertension. The most commonly used agents in this situation are sodium nitroprusside (Nipride) and labetalol (Normodyne). As already mentioned, emergency medical therapy may be needed for patients with severe (malignant) hypertension. In addition, emergency treatment of hypertension may be necessary in patients with short duration (acute) congestive heart failure, dissecting aneurysm (dilation or widening) of the aorta, stroke, and toxemia of pregnancy.

1.4.1.5 Treatment during pregnancy:

Women with hypertension may become pregnant. These patients have an increased risk of developing preeclampsia or eclampsia (toxemia) of pregnancy. These conditions usually develop during the last three months (trimester) of pregnancy. Preeclampsia, which can occur with or without pre-existing hypertension, affected women have hypertension, protein loss in the urine (proteinuria), and swelling (edema). In eclampsia (toxemia), convulsions also occur and the hypertension may require prompt treatment. The foremost goal of treating the high blood pressure in toxemia is to keep the diastolic pressure below 105 mmHg in order to prevent a brain hemorrhage in the mother.

Hypertension that develops before the 20th week of pregnancy almost always is due to pre-existing hypertension and not toxemia. High blood pressure that occurs only during pregnancy, called gestational hypertension, may start late in the pregnancy. These women, however, do not have proteinuria, edema, or convulsions. Furthermore, gestational hypertension appears to have no ill effects on the mother or the fetus. This form of hypertension resolves shortly after delivery, although it may recur with subsequent pregnancies.

The use of medications for hypertension during pregnancy is controversial. The key question is, "At what level should the blood pressure be maintained?" For one thing, the risk of untreated mild to moderate hypertension to the fetus or mother during the relatively brief period of pregnancy probably is not very large. Furthermore, lowering the blood pressure too much can interfere with the flow of blood to the placenta and thereby impair fetal growth. So, some sort of a compromise must be met. Accordingly, not all mild or moderate hypertension during pregnancy needs to be treated with medication. If it is treated, however, the blood pressure should be reduced slowly and not to very low levels, perhaps not below 140/80 mmHg.

The anti-hypertensive agents used during pregnancy need to be safe for normal fetal development. The beta-blockers, hydralazine (an old vasodilator), labetalol, alpha methyldopa and more recently, the calcium channel blockers have been advocated as suitable medications for hypertension during pregnancy. Certain other anti-hypertensive medications, however, are not recommended (they are contraindicated) during pregnancy. These include the ACE inhibitors, the ARB drugs, and probably the diuretics. ACE inhibitors may aggravate a diminished blood supply to the uterus (uterine ischemia) and cause kidney dysfunction in the fetus. The ARB drugs may even lead to death of the fetus. Diuretics can cause depletion of the blood volume and so impair placental blood flow and fetal growth.

1.4.1.6 Antihypertensive drugs [33]:

These drugs are used to lower BP in hypertension. Systemic arterial BP is determined by cardiac output (c.o.) and total peripheral resistence (t.p.r.). In most of the cases, rise in BP is due to increase in t.p.r. while c.o. and heart rate are not high. The cutoff manometric reading between normotensive and hypertensive is arbitrary. For

practical purpose "hypertension" could be that level of BP at or above which long term antihypertensive treatment will reduce cardiovascular mortality. The WHO ISH guidelines (1999) have defined it to be 140 mmHg systolic and 90 mmHg diastolic, though risk appears to increase even above 120/80 mmHg. In fact, no clear cut lowest limit has been established. Epidemiological studies have confirmed that higher the pressure (systolic or diastolic or both) greater is the risk of cardiovascular disease.

Majority of cases are of essential (primary) hypertension, i.e. the cause is not known. Sympathetic and rennin-angiotensin system may or may not be overactive, but they do not contribute the tone of blood vessel and c.o. in hypertensives, as they do not normotensives. Many antihypertensive drugs interfere with these regulatory systems at one level or the other. Antihypertensive drugs, by chronically lowering BP, may reset the barostat to function at a lower level of BP.

Classification of anti hypertensive drugs:

1. ACE inhibitors:
   Captopril, Enalpril, Lisinopril, Perindopril, Ramipril

2. Angiotensin (AT1) antagonists:
   Losartan, Candesartan, Irbesartan

3. Calcium channel blocker:
   Verapamil, Diltiagen, Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lecidipine

4. Diuretics:
   Thiazides:- Hydrochlorothiazide, Chlorthalidone, Indapamide,
   High ceiling:- Furesomide, etc.
   K^+sparing:- Spironolactone, Triamterine, Amiloride,
5. β Adrenergic blockers:
   Propranolol, Metoprolol, Atenolol, etc.

6. β+ α Adrenergic blockers:
   Labetalol, Carvedilol

7. α Adrenergic blockers:
   Prazocine, Terazocine, Doxazosine, Phentolmine, Phenoxybenzamine

8. Central sympatholytics:
   Clonidine, Methyldopa

9. Vasodialators:
   Arterioler:- Hydralazine, Minoxidile, Diazoxide
   Arterioler + Venus: - Sodium Nitroprusside

1.4.1.7 β-adrenergic blockers [34]:

β-adrenoceptor blocking drugs are widely used for the treatment of cardiovascular diseases such as arterial hypertension, coronary heart disease and supraventricular and ventricular tachyarrhythmias. They may also be beneficial in the hyperkinetic heart syndrome, hypotensive circulatory disorders, portal hypertension, hyperthyroidism, tremour, migraine, anxiety, psychosomatic disorders or glaucoma. In recent years even patients with heart failure have been successfully treated with β-blockers initially given at very low doses.

A great number of β-adrenoceptor blocking drugs are now available for clinical uses which differ widely with respect to their pharmacodynamic and pharmacokinetic properties. They all interact with β-adrenoceptors forming drug receptor complexes so that endogenous norepinephrine and epinephrine are hindered from accessing the receptor. This leads to a competitive antagonism which is characterized by a parallel shift of the concentration-response curve of the agonist to the right. The β-receptor blockade can be completely reversed by high concentrations of the agonist. The various β-blockers differ with respect to their β-receptor affinity, β1-selectivity, partial agonist activity and physicochemical properties (lipophilicity, stereospecificity) which all may be of particular importance for clinical use. In addition, pharmacokinetic properties such as absorption, bioavailability, metabolism, volume of distribution and elimination (hepatic and/or renal clearance) may guide therapy in special patients.

Pharmacodynamic properties:

In many organs there is a coexistence of β1 and β2-receptors. For example; in the normal human heart about 80 % of the β-receptors are of the β1-subtype. In heart failure β1-receptors are down-regulated so that a relatively higher proportion of β2-receptors can be measured. The physiological and therapeutic actions of a β-blocker depend on the actual density of β1 and/or β2-receptors in the different organs, on the affinity of the β-blocker and on the local drug concentration.

Table 1.3: Pharmacodynamic properties of β–blockers:

Affinity (pA_2-values)								
β–blockers	**Chronotropy**	**Inotropy**	**Trachea**	**β 1-Selectivity**	**Sel. Index**	**PAA**	**PC**	**UMA**
Acebutolol	7.3	7.0	6.4	+	0.9	+	0.17	(+)
Alprenolol	8.6	8.6	8.4	-		+	3.3	+
Atenolol	7.6	7.4	5.9	+	1.7	-	0.0033	-
Betaxolol	8.6	8.6	6.2	+	2.4	-	3.9[1])	(+)
Bisoprolol	8.8	8.9	6.4	+	2.4	-	3.0	+
Bopindolol	9.51[2])	9.37[2])	9.65[2])	-		(+)		
Carazolol	9.9	9.8	9.4	-		-	13.7	+
Carteolol[4])	9.2	9.0	9.3	-		+	0.214	(+)
Carvedilol[4])	9.1		8.87	-		-	226[1])	(+)
Celiprolol	7.6	8.1	6.8	+	0.8	+	0.152	(+)
Esmolol[5])	6.9	6.9	5.3	+	1.6	-		-
Mepindolol	9.9	9.5	9.0	-		+	0.54	(+)
Nadolol	7.9	7.2	7.5	-		-	0.008	-
Nebivolol[4])	8.24		5.77	+	2.47	-		+
Oxprenolol	8.5	8.7	8.5	-		+	0.51	(+)
Penbutolol[3])	8.6	8.9	9.0	-		(+)	50.0[1])	+
Pindolol	9.2	9.4	9.0	-		+	0.20	(+)
Propranolol	8.4	8.5	8.5	-		-	5.4	+
Sotalol	6.1	5.9	5.9	-		-	0.011	-
Timolol	8.7	8.7	8.2	-		-	0.28	(+)

Sel. index = selectivity index: pA_2 chronotropy minus pA_2 trachea;
PAA = partial agonist activity; PC = partition coefficient (n-octanol/phosphate buffer) (temperature 20-30^{0}C, pH 7.0); [1]) pH 7.4; [2]) active metabolite; [3]) S-isomers; [4]) vasodilative; [5]) only i.v. –application; UMA = unspecific membrane action; + = positive effect; - = no effect.

Affinity:

β-blockers with high affinity for β-adrenoceptors are effective in small doses if their bioavailability is not too low. Their action still continues even if they are washed out of the extracellular space. Consequently their duration of action cannot be predicted by the plasma half life of the β-phase of elimination. This holds true for many drugs with high affinity for β-adrenoceptors and short plasma half life (2–4 hours for the β-phase). Penbutolol, for example, has a high affinity for β-adrenoceptors, dissociates slowly from the β-receptor, the $t^{1/2}$ value (β-phase) is about 2 hours, the terminal half life is about 27 hours and the duration of action after a 40 mg dose amounts to about 48 hours.

Physico-chemical properties:

Lipophilicity:

β-blockers may be divided into lipophilic or hydrophilic drugs according to their distribution coefficient. Atenolol, nadolol or sotalol are hydrophilic, penbutolol or propranolol are lipophilic whereas bisoprolol or betaxolol are in intermediate position. The following parameters are dependent on lipophilicity:

1) duration of β-receptor blockade,
2) metabolism or renal elimination (pharmacokinetics),
3) diffusion through biological barriers (eg, blood/brain, placenta) and
4) tissue concentration (especially during intoxication).

Hydrophilic β-blockers like atenolol are advantageous in patients who suffer from central nervous side effects during therapy with lipophilic drugs (sleep disturbances, psychosis, depression, hallucination)

Stereospecificity:

With the exception of penbutolol or timolol all the β-blockers are racemic mixtures containing 50 % of the β-receptor blocking S-isomer and 50 % of the R-isomer which is without β-blocking action. Introduction of the pure S-form into the market is without clinical significance as there is no evidence that concomitant application of the S- and R-form leads to a higher rate of side effects.

Pharmacokinetic properties:

Pharmacokinetic differences of β-adrenoceptor blocking drugs (Tables 1.4) with respect to absorption in the gastrointestinal tract, liver metabolism, plasma protein

binding, volume of distribution and renal or biliary elimination play an important role for those patients in whom these parameters are altered by their disease. Especially disturbances of hepatic and/or renal clearance may be of clinical significance either for the choice of the appropriate drug or for the dose regimen of a given drug.

Table 1.4: Pharmacokinetic properties of β–blockers:

β – blockers	$t^{1/2}$ (h)	Bioavailability (%)	First pass effect	V_d (l/kg)	Total clearance (ml/min)	Renal clearance (ml/min)
Acebutolol	7-13	40-60	+	1.35	600	200
Alprenolol	2-3	10-30	+	3.3	1200	0
Atenolol	6-9	50	-	0.7	100-800	100-170
Betaxolol	14-20	80	-	6.0	326	47
Bisoprolol	10-12	88	-	3.2	257	140
Bopindolol	10-14	60-70	+	2.9	515	?
Carazolol	85	< 10	+	10.9	35005	105
Carteolol	7	90	-	3.6	650	277
Celiprolol	5	50	-	6.5	850	150
Mepindolol	4.2	> 95	-	5.7	650	0
Nadolol	14-24	20-30	-	2.5	110	67
Nebivolol	22	12	+	?10	860	7.4
Oxprenolol	1-3	24-60	+	1.3	600	0
Penbutolol	1-36	> 90	-	0.3	350	0
Pindolol	3-4	90	-	2.0	400	163
Propranolol	3-4	30	+	3.6	1000	0
Sotalol	15	75-90	-	2.0	120	120
Timolol	5.5	50-75	+	1.4-3.5	560	70-109
Talinolol	12	55	-	3.3	343	196

+ = positive effect; - = no effect.

REFERENCE

1. Parmar NS. and Shivprakash. Biopharmaceutical and Pharmacokinetic Considerations in the Development of Controlled Release Drug Products. In: Controlled and Novel Drug Delivery, Jain NK, ed. CBS Publishers and Distributors: New Delhi; 1st Edn. 1997, 1-25.

2. Gupta R. and Mukherjee B. Development and *in vitro* evaluation of diltiazem hydrochloride transdermal patches based on povidone-ethylcellulose matrices. *Drug Dev. Ind. Pharm.* 2003; **29(1)**: 1-7.

3. Das MK, Bhattacharya A. and Ghosal SK. Transdermal delivery of trazodone hydrochloride from acrylic films prepared from aqueous latex. *Indian J. Pharm. Sci.* 2006; **68(1)**: 41-46.

4. Misra A. Transdermal drug delivery: present and future. *The Pharma Review.* 2004; Jul-Aug: 92-102.

5. Sagar P, Kulkarni RV. and Doddayya H. Development and evaluation of membrane controlled transdermal therapeutic systems. *The Pharma Review.* 2006; April: 90-92.

6. Barry BW. Dermatological Formulations Percutaneous Absorption. Marcel Dekker, Inc: New York; 1st Edn. Vol. **18**, 1983, 1-40.

7. http://www.managedcaremag.com, MANAGED CARE April 2004. ©MediMedia USA

8. Barry B. Transdermal Drug Delivery. In: Pharmaceutics The science of Dosage Form Design, Aulton ME, ed. Harcourt Publishers Limited: London; 2nd Edn. 2002, 500-533.

9. Franz TJ, Tojo K, Shah KR. and Kydonieus A. Transdermal Delivery. In: Treatise on Controlled Drug Delivery, Kydonieus A, ed. Marcel Dekker, Inc.: New York; 1st Edn. 1992, 341-415.

10. Chien YW. Novel Drug Delivery Systems. Marcel Dekker, Inc.: New York; 2nd Edn. 1992, 301-75.

11. Sood R. and Jayaswal SB. Transdermal controlled release drug administration. *The Eastern Pharmacist.* 1987; September: 47-52.

12. Kligman AM. A biological brief on percutaneous absorption. *Drug Dev. Ind. Pharm.* 1983; **9**: 521-560.

13. Klemsdal TO, Gjedsdal K. and Bredesen JE. Heating and cooling of the nitroglycerin patch application area modify the plasma level of nitroglycerin. *Eur. J. Clin. Pharmacol.* 1992; **43**: 625-628.

14. Potts RO, Buras EM. and Chrisman DA. Changes with age in moisture content of human skin. *J. Invest. Dermatol.* 1984; **82**: 97-100.

15. Wester RC. and Maibach HI. Regional Variation in Percutaneous Absorption. In Topical Absorption of Dermatological Products. Bronaugh RL. and Maibach HI, eds. Marcel Dekker, Inc.: New York; 1st Edn. 2002; 33-41.

16. Martin R, Denyer SP. and Hadgraft J. Skin metabolism of topically applied compounds. *Int. J. Pharm.* 1987; **39**: 23-32.

17. Ledger PW. Skin biological issues in electrically enhanced transdermal delivery. *Adv. Drug del. Rev.* 1992; **9**: 289-307.

18. Peck KD, Hsu J, Li SK, Ghanem AH. and Higuchi WI. Flux enhancement effects of ionic surfactants upon passive and electroosmotic transdermal transport. *J. Pharm. Sci.* 1998; **87**: 1161-1169.

19. Pikal MJ. The role of electroosmotic flow in transdermal iontophoresis. *Adv. Drug Del. Rev.* 1992; **9**: 201-237.

20. Lu FM *et al.* The effect of formulation variations on iontophoretic transdermal delivery of leuprolide to humans. *Drug Dev. Ind. Pharm.* 1993; **19**: 1557-1571.

21. Hoogstrate AJ, Srinivasan V, Simms SM. and Higuchi WI. Iontophoretic enhancement of peptides: behavior of leuprolide versus model permeants. *J. Control. Rel.* 1994; **31**: 41-47.

22. Delgado-Charro MB, Rodriguez-Bayon A. and Guy RH. Iontophoresis of nafarelin: effects of current density and concentration on electrotransport *in vitro*. *J. Control. Rel.* 1995; **35**: 35-40.

23. Rautio J, Taipale H, Gynther J, Vepsalainen J, Nevalainen T. and Jarvinen T. *In vitro* evaluation of acyloxyalkyl esters as dermal prodrugs of ketoprofen and naproxen. *J. Pharm. Sci.* 1998; **87**: 1622-1628.

24. Ansel HC, Allen Jr. LV. and Popovich NG. Pharmaceutical Dosage Forms and Drug Delivery Systems. Lippincott Williams and Wilkins: Philadelphia; 7th Edn. 1999, 263-277.

25. Chien YW. Novel Drug Delivery Systems. Marcel Dekker, Inc.: New York; 2nd Edn. 1992, 797-802.

26. Brahmankar DM. and Jaiswal SB. Biopharmaceutics and Pharmacokinetics- a treatise. Vallabh Prakashan: Delhi; 1st Edn. 1995, 365-368.

27. Sridevi S. and Krishna DR. Transdermal Drug Delivery Systems. *The Eastern Pharmacist.* 1991; October: 17-24.

28. Chien YW. Transdermal Therapeutic sustems. In: Controlled Drug Delivery: Fundamentals and Applications, Robinson JR. and Lee VHL, eds. Marcel Dekker, Inc.: New York; 2nd Edn. 1987, 524-549.

29. Li W. Transdermal delivery systems – recent progress in research and development. Johnson & Johnson pharmaceutical research and development. *Future Drug Delivery.* 2006.

30. Finnin BC. and Morgan TM. Transdermal penetration enhancers: applications, limitations, and potential. *J. Pharm. Sci.* 1999; **88(10)**: 955-958.

31. Rang HP, Dale MM. and Ritter JM. Pharmacology. 4th Edn. Harcourt Publishers Limited, London. 1999; 293-299.

32. (April, 2006-2007).

33. Tripathi KD. Essentials of Medical Pharmacology. Jaypee Brothers Medical Publishers (p) Ltd. New Delhi, 2003; 5th Edn., 486-518.

34. Borchard U. Pharmacological properties of beta-adrenoceptor blocking drugs. *J. Clin. and Basic Cardiol.* 1998; **1 (Issue 1)**: 5-9.