Introduction
1. INTRODUCTION

Painless, rapid, controlled and noninvasive molecular transport of the therapeutic molecules to the target area of drug action is of widespread interest in modern therapy (Herndon et al., 2004). In this context, transdermal drug delivery (TDD) remained a focus of research interest for the last two decades. The TDD is projected to be an alternative to the intra venous (IV) infusion, which can maintain the plasma level to the safe desired level and can reduce the side effects of therapy. This route is particularly beneficial for the drugs which need to be administered in chronic diseases. The route can control hypertension being one of the physiological syndromes that leads to major cardiovascular emergencies more successfully. Infact, the data obtained from Catapress TTS, the transdermal clonidine has confirmed this theory. A detailed study based on retrospective analysis of the Medicaid claims in two American states, Florida and Carolina had shown that, while the prescription expenditure of the patients using the patch was significantly higher, it saves them from hospitalization and diagnostic costs and reduces the overall health expenditure (Sclar et al., 1991). The revelations have given the transdermal research the much needed impetus. In the last decade, 40% of the drug delivery candidates under clinical evaluation in United States (US) belonged to the transdermal category (Cross and Roberts, 2004).

1.1 TRANSDERMAL DRUG DELIVERY SYSTEMS (TDDS)

The TDDS is defined as a delivery device, which upon application on a suitable skin surface will be able to deliver the drug to the systemic circulation at a sufficient concentration to ensure therapeutic efficacy. TDDS are ideally suitable for drugs that need to be administered for diseases those are chronic in nature. The inherent drawback of hepatic first pass elimination greatly reduces the effective drug concentration in the systemic circulation, leading to administration of high doses of conventional dosage formulations. This can be eliminated by IV infusion at preprogrammed rate. The IV infusion can bypass the first pass effect by administering the drug directly to the venous circulation. It can also eliminate the fluctuations in drug concentration in the blood, but it needs hospitalization of patients and close medical supervision, making it quite expensive and impractical for long term therapy (Chien, 1987).
1.1.1 ADVANTAGES OF THE TDDS OVER THE OTHER DRUG DELIVERY SYSTEMS

Hypertension is a disorder, equally prevalent in the developed and the undeveloped countries. An analysis shows that cardiovascular disease (CVD) was responsible for the highest mortality rate and a mild hypertension may be the humble beginning for the fatal cardiovascular ailments (Collins et al., 1996).

Epidemiological studies have also proved that, normalization of blood pressure (BP) plays a primary role in the prevention of cardiovascular mortality and morbidity. Though a large number of antihypertensives, both natural and synthetic are available in the market, most of these conventional oral dosage forms have certain limitations. These conventional oral dosage forms introduce the drugs to gastrointestinal tract (GIT), which offers extended surface area for drug absorption. Though most of the drugs are completely absorbed, the bioavailability is much reduced due to extensive first-pass effect (Hoffman and Lefkowitz, 1996).

In addition to the first pass effect, the fluctuations in plasma concentration can affect the arterial pressure adversely. A number of drugs show excessive first dose syndrome and their effective concentration vary extensively among individuals due to enzyme induced deactivation. To maintain the arterial pressure within the normal physiological range, it is necessary to have the concentration always on upside of the minimum effective concentration and only a continuous controlled supply of the drug from a reservoir can ensure maintenance of the constant plasma level. To achieve this goal, a number of antihypertensive agents have been marketed as sustained release (SR) drug delivery systems (e.g., Metoprolol, Clonidine, Verapamil, Felodipine, Diltiazem, Propranolol, Nifedipine) (Frishman and Lazar, 1992). Studies have shown that these dosage forms can maintain the effective concentration for a prolonged period by controlling the supply of the drug from the drug reservoir either by control of dissolution or diffusion. But ultimately, these oral dosage forms cannot be prolonged beyond 24-36 h because of limited gastric residence time (GRT). The presence of food and behavior of the patient may also affect the release profile and drugs, which are absorbed through a particular absorption window, are not good candidates for these types of dosage forms. But the single most factors that makes the development of such type of dosage form, a
debatable issue is the hepatic metabolism or first-pass effect. Bioavailability of the drugs that shows the saturable first-pass effect are much reduced in the prolonged release dosage form because of enhanced hepatic metabolism. Since there was evident need for a controlled release noninvasive dosage form that will able to be delivering these drugs for weeks altogether, research on the transdermal route got an impetus. TDD is considered to be the ideal method, which can bypass the first-pass elimination, absolute elimination of GIT toxic effects, maintain the steady plasma level of drug for a prolonged period and deliver the drug at predetermined rate without the hazards of specialist care as is required in the IV infusion (Chong and Fung, 1989). Other advantages of TDDS include

- Prevents toxic action of drugs with short therapeutic index
- Reduce frequency of drug administration
- Easily terminated by simple removal from the skin surface
- Permits use of potent drug with short biological half life and
- The improved patient compliance.

1.1.2 HISTORY AND PRESENT STATUS OF TDDS

The potential of TDD utilizing the huge area of skin surface administration has been conceptualized in the ancient times when medicated plasters were developed. These plasters were made of natural adhesives in which the drugs were dispersed. The adhesive dispersed system was fixed on a strong backing support. The adhesive was formulated to get an optimum adhesive strength to stick to the skin and make a close contact with it so that the drug delivery is transdermal delivery (Chien, 1992).

Though little has been known from the literature survey, it has been observed that those types of plasters were popular in ancient China. A few of them are still available in the market, one of those is ‘Yang-Chang’ and consists of multiple ingredients of herbal origin for topical application. The components in the plasters includes, Fossilia oasis mastoid, Eupolyphagus inensis Walker, Sanguis Draconis, Catechu, Myrrha, Rhizoma drynariae, Radix dipsaci, Flos carthami, Rhizoma rhei, Herba taraxaci, Mentholum and Methylis salycylas. This plaster was indicated for analgesic action in the muscle and to promote healing of bone features. The active ingredients of herbal drugs were supposed to penetrate the skin, when it was applied to the skin.
Medicated plaster is also popular in Japan as over the counter pharmaceutical dosage form and is known as Cataplasm. One of those is Salonpas. Although this is also a multi ingredient plaster, unlike the Chinese plaster it contains the pure drugs. The compositions in salonpas are methyl salicylate, 1-menthol, camphor, glycol salicylate, thymol and tocopherol acetate.

Medicated plasters have also existed in western medicine for the last several decades. Three medicated plasters have been documented in official compendium. Those are belladonna plaster, mustard plaster and salicylate plaster. These types of medicated plasters are also available now in Indian market. One medicated plaster containing 40% salicylic acid indicated, as corn remover is available in Indian market (corn cap). Here a strong contrast to be noted is that the western medicated plasters are mostly composed of a single ingredient, whereas the plasters used in ancient china and Japan are multicomponent, and are of herbal origin. But the common feature is that all the medicated plasters have been developed for topical use (Chien, 1987).

The first TDDS was introduced in the US over 20 years ago. The technology generated tremendous excitement and interest amongst the major pharmaceutical companies in the 1980s and 90s. Excitement dwindled to disappointment, when the limitations of the existing transdermal technology became evident and the numbers of drug candidates were limited to very few molecules. Factors limiting the success of transdermal technology included such things as local skin irritation associated with certain drugs and formulations, limitation on the dose of drug that could be delivered transdermally, a lag time associated with the delivery of the drug across the skin, variation of absorption rate based on site of application, skin type and patient age, and variation in adhesive effectiveness across skin types. These limitations, in addition to the rise in other non-oral drug delivery systems, such as pulmonary delivery systems, caused interest in transdermal technology to decline. Without the interest of big pharma and the funding partnerships that it provided, few TDD companies could sustain themselves without a large pipeline that led products to the market place. By the mid to late 1990s, the trend of TDD companies merging into larger organizations (i.e., J&J acquiring ALZA and a part of Cygnus, Watson acquiring Theratech, and Elan acquiring Sano) combined with the increasing number of mega-pharmaceutical mergers, left fewer companies that
wanted to develop transdermal products. Acceptance of transdermal technology by larger pharmaceutical companies became more conservative, and development efforts remained focused on oral drug delivery (Cleary and Beskar, 2003).

Interest in transdermal has increased on several fronts over the past several years. Technology companies have generated additional clinical data demonstrating the potential of advanced transdermal technology. More than 20 transdermal patches, with 13 drug molecules are already available in the market. However the small group of marketed products has represented drugs of many important classes; antianginal (nitroglycerin, isosorbide dinitrate), antihypertensive (clonidine), antiemetics (scopolamine), hormones (estradiol, norethindrone acetate, norelgestromin, testosterone), urinary antispasmodic (oxybutynin), local anesthetic (lidocaine, prilocaine) and central nervous system (CNS) drugs (fentanyl, nicotine). Although there are only a limited number of marketed transdermal patches available, many others are in development or awaiting food and drug administration (FDA) approval (Wilkosz and Bogner, 2004). Noven Pharmaceuticals has recently submitted a new drug application for a methylphenidate transdermal patch. There is also a great deal of investigation into an insulin transdermal delivery system (TDS). Some other drugs that are being investigated for transdermal use include albuterol, enalapril, dronabinol, ketorolac, alprazolam, cytarabine, atenolol, buprenorphine, selegiline, isosorbide dinitrate, and prazosin.

Improvement in physical and chemical permeation enhancement technologies also led to renewed interest in transdermal drug delivery. Products have already reached the US market using iontophoresis (e.g. lidocaine in the Iomed’s Iontocaine and epinephrine in the Phoresor iontophoresis system), which is marketed for local dermal analgesia. Similarly, Vyteris is awaiting approval for its iontophoretic system, which also delivers lidocaine for dermal anesthesia in children. Several other companies have completed various stages of clinical iontophoresis studies, most notable among them being ALZA with its E-TRANS system using fentanyl for the management of postoperative pain. Companies, such as Altea Therapeutics, Transpharma, and ALZA are using various microporation technologies to transdermally deliver peptides and proteins, vaccines, and various pain medications. Initial clinical results are encouraging and have helped bring greater attention to the potential of active transdermal technology. Clinical development
continues in systems utilizing electroporation, sonophoresis, and electronic component integrated technologies (Cleary and Beskar, 2003).

1.1.3 CLASSIFICATION OF TDDS

Several drug delivery systems have been developed to achieve rate controlled transdermal delivery of drugs for the last one decade. Those can be classified into four basic types (Chien, 1992).

i) Membrane diffusion controlled TDDS

In this type of TDDS, the drug reservoir may be i) A solution of drug in an unleachable (viscous liquid) solvent e.g. alkyl alcohol or ii) A solid dispersed homogenously in a solid polymer matrix e.g. polyisobutylene adhesive or iii) a solid suspended in an unleachable viscous liquid medium e.g. silicone fluid. The drug reservoir is encapsulated between an impermeable metallic or plastic laminate and porous or nonporous polymeric membrane. A layer of bioadhesive material is applied on the releasing membrane for intimate contact with the skin surface. The adhesive is perfectly biocompatible, hypoallergenic, pressure sensitive (e.g. poly isobutylene or silicon adhesive). The rate of drug release can be controlled in a pre programmed manner by the following methods

a) By changing the thickness of the rate controlling membrane
b) By changing the composition of the drug reservoir
c) By changing the composition of the rate controlling membrane
d) By changing the permeability coefficient of the rate controlling membrane

A number of TDDS have been developed and markets successfully utilising this technology e.g. Transderm Scop by Ciba, Transderm Nitro by Ciba, Catapress TTS by Boehringer Ingelheim and Estraderm.

ii) Adhesive dispersion type TDDS

This type of TDDS is a simplified form of the membrane permeation controlled type with out the controlling membrane. In this system, the drug reservoir is formulated by dispersing the drug in a suitable adhesive polymer e.g. polyisobutylene or poly acrylate. This dispersion is then spread on the backing layer. This can be done by two processes, namely solvent casting method and melting method.
The release of drug from this system can be controlled by
a) Changing the thickness of the adhesive layer
b) Changing the composition of the adhesive layer and
c) Changing the concentration in the adhesive layer.

A number of TDDS of this type have been developed and marketed. Some of them are Frandol, Nitrodur II system and Deponit.

iii) Matrix diffusion controlled TDDS

This is a much simplified form of TDDS. In this system the drug reservoir is formed by homogenously dispersing the drug in a suitable polymeric matrix. The polymer may be a hydrophilic or lipophilic nature, may be a mixture of both in a optimum proportion. The polymeric disc, is then fixed on a drug – impermeable backing, which may be a plastic or polymeric sheets having sufficient mechanical strength. In this system adhesive is spread around the drug releasing surface instead of applying it in the whole surface. The release of the drug can be controlled by

a) Changing the composition of the polymeric matrix
b) Changing the thickness of the polymeric matrix
c) Changing the drug loading in the matrix
d) Changing the proportion of plasticizers in the matrix.

This technology has been successfully utilized to develop and market a number of TDDS. They are Nitrodur system and NTS system.

iv) Micro reservoir dissolution controlled TDDS

This is a combination of the membrane diffusion controlled and matrix dispersion controlled system. In this system, the drug reservoir is mounted on a drug impermeable backing, which is mounted on a adhesive pad. The drug reservoir is formulated by a three step process. First the drug is suspended in an aqueous solution of a water soluble polymer like poly ethylene glycol. Next, this suspension is dispersed in a lipophilic polymer, to form an unleachable microscopic drug reservoir. This is done, using a high mechanical shear stress. Finally the thermodynamically unstable system is quickly stabilized by immediate cross linking of the polymeric chain in situ. A medicated polymeric disc of a certain thickness and surface area emerged. This system is quite complicated and has several control steps to monitor the release of drug from the system.
A system with a pre programmed rate can be developed by optimizing the following factors

a) The composition of micro reservoir
b) Process variables possible during micro reservoir formulation
c) Selection of the polymer for external phase
d) Elaborate process and agents

The technology has been successfully utilized for the development and marketing nitroglycerin containing TDDS. E.g. Nitro disc

1.2 THE SKIN: AS A NOVEL ROUTE

The skin is the largest and most versatile organ of the human body, with surface area of about 2m² and receives approximately one third of all blood circulating through the body (Singh and Singh, 1993). It is composed of an outer epidermis, and inner dermis and the underlying subdermal tissue (Fig.1). The epidermis is divided in to two parts, nonviable epidermis over the stratum corneum (SC) and viable epidermis, which includes four other layers of the epidermis, viz., stratum lucidum, stratum granulosum, stratum spinosum, and stratum germinativum. Historically, the skin as thought to be totally impervious to exogenous chemicals. The intact SC, an effective deterrent to transepidermal water loss, for simplicity sake it can be compared to a ‘brick and mortar’ of which hydrated keratin comprise the ‘bricks’, embedded in a ‘mortar’, composed of multiple lipid bilayers of ceramides, fatty acids, cholesterol and cholesterol esters. These bilayers form regions of semicrystalline, gel and liquid crystals domains (Barry, 2004).

The viable epidermis is an aqueous solution of protein encapsulated into cellular compartments by thin cell membranes, which are fused together by tonofibrils. The dermis is 0.2-0.3 cm thick and is made of a fibrous protein matrix, mainly collagen, elastin, and reticulum, embedded in an amorphous colloidal ground substance (semigel matrix of micropolysaccharides). The skin surface also contains has several types of appendages. These include hair follicles with sebaceous glands, eccrine and apocrine sweat glands, and the nails. An average human skin surface is known to contain, on the average, 40-70 hair follicles and 200-250 sweat ducts per square centimeter of the skin. However, these skin appendages occupy only 0.1 % of the total human skin surface. Initially skin was thought to be an inert organ devoid of metabolic activities, but the
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recent finding shows that skin has enzymatic activity, including cytochrome p450 isozymes which may be localized to specific cell types, especially in the epidermis and pilosebaceous system. Enzymes identified in the SC include those with lipase, protease, phosphatase, sulphatase and glycosidase activity (Singh and Singh, 1993).

![Diagram of skin structure and macro routes of drug penetration.](image)

Figure 1: Diagram of skin structure and macro routes of drug penetration: (1) via the sweat ducts; (2) across the corneum or (3) through the hair follicles.

Xenobiotic substances are first chemically activated by oxidation with the involvement of cytochrome P450 isozymes. These enzymes are localized mainly in the endoplasmic reticulum and the activity is highest in the microsomal fraction of skin homogenates. The catalytic activity of the enzymes in the hair follicles is particularly high. While the epidermal activity of the P450 in skin are only about 1-5 percent of those in the liver, the transferase activity in the skin can be as high as 10 percent of hepatic values. The total skin blood flow is only about 6.25 percent of the total liver blood flow (Banga, 1998). Thus the metabolism is lower in skin though the spectrum of reactions in the skin is similar to that observed in the liver. The enzymatic activity of the skin varies with the anatomical site. For instance, hydrocortisone 5α-reductase activity was detected only in human foreskin while high levels of testosterone 5α-reductase were found in the
scrotal skin. The distribution of enzymatic activity within the various skin layers is not well known owing to difficulties with the experimental methodologies. As blood capillaries lie just under the epidermis-dermis junction, drugs may only have minimal contact with dermal enzymes before they are taken up by the general circulation. Thus, the enzymatic activity of the epidermis may be more important as a barrier to drug absorption. The enzymatic hydrolysis of drugs in the skin has been reported and may differ between \textit{in vivo} and \textit{in vitro} conditions (Banga, 1998).

\subsection*{1.2.1 PERCUTANEOUS ABSORPTION}

The phenomenon of diffusive penetration of drugs and chemicals through skin is known as percutaneous absorption. Administration of chemical agents to the skin surface has long been practiced, whether for healing or purely decorative or cosmetic purposes. Though the mechanism of penetration was poorly understood. Molecules moving from the environment must compromise the barrier of SC then the viable epidermis, and finally enter into the blood through the capillary. The diffusion mechanism through the horny layer is basically a passive process. The viable tissue layers of epidermis and the capillaries are relatively permeable and the peripheral circulation is sufficiently rapid so that, for the majority of drugs, diffusion through the SC is the rate-limiting step (Idson, 1975). Passage into skin occurs through two main paths: the transepidermal and transappendageal (Fig.1 and 2). The transcellular area is about 99%, the trans follicular pathway is about 0.3%, where as the intercellular pathway occupies nearly 0.7%. The diffusional pathlengths for three routes are 25 μm, 200 μm and 359 μm.

\textbf{i) Transepidermal absorption}

The SC and the uppermost layers of living epidermal cells determine transepidermal absorption. Transdermal drug permeation through the SC can take place between the cells (intercellular) or through the protein filled cells (transcellular route). The relative contribution of these routes depends on the solubility, partition coefficient and diffusivity of the drugs within these protein or lipid phases. The barrier function is equally efficient for both outward and inward passage. The uppermost layer of the SC provide little barrier function because of greater cellular permeability and wider intercellular spaces, permitting free permeation of anions, cations and large molecules. The deep layers of SC show a closer package of cells acting as the barrier layers. Once
the SC is compromised, there is apparently no significant hindrance to the permeation of the remaining layers. Polar and non-polar substances diffuse through the SC by different mechanisms. The polar molecules diffuse principally through a polar pathway consisting of bound water within the extensively hydrated SC. Non-polar molecules dissolve and diffuse through the non aqueous lipid matrix of the SC.

ii) Transappendageal absorption

The three possible pathways for permeation through appendages are: through the wall of hair follicles, through the sweat glands and through the sebaceous glands. Diffusion through the pilosebaceous units and sweat glands is often referred to as shunt diffusion. Each hair follicle has one or more connecting sebaceous glands, which empty their secretion into the follicular canal near the skin surface. Drug substances applied to the skin surface reach the orifices of the sweat glands and the hair follicles directly. Therefore, the most likely pathway via the transfollicular route is through the microscopic spaces between the hair shaft and the follicular wall. These spaces permit the passage of substances into areas below the membrane barrier (Ritschel and Hussain, 1988).

Figure 2: Diagram of stratum corneum and two microroutes of drug penetration.
1.2.2 THEORETICAL BASIS OF PERCUTANEOUS ABSORPTION

The passive diffusion of a non-electrolyte in the absence of any bulk flow is expressed by Fick’s first law of diffusion as

\[ J = -D \frac{dC}{dx} \]  
(Equation 1)

Where \( J \) is the flux, \( D \) is the diffusion coefficient and \( \frac{dC}{dx} \) is the concentration gradient over a distance \( x \). Fick’s first law of diffusion can be used to describe the skin permeation of drugs, however the concentration gradient across the skin tissue cannot be easily measured but can be approximated by the product of the permeability coefficient (\( K_p \)) and the concentration difference across the skin (\( C_s \)). The steady state transdermal flux, \( J_{ss} \), through the skin barrier is thus given as:

\[ J = K_p C_s \]  
(Equation 2)

Where \( K_p \), the permeability coefficient, is defined by:

\[ K_p = \frac{P.D}{h} \]  
(Equation 3)

Where \( P \) is the partition coefficient and \( h \) is the thickness of the skin. The cumulative amount of drug permeating the skin (\( Q_1 \)) is given by:

\[ Q_1 = \frac{P.D.C_s}{h} \left( t - \frac{h^2}{6D} \right) \]  
(Equation 4)

Where \( C_s \) is the saturated reservoir concentration when a sink condition is maintained in the receptor solution. Differentiation of the equation 4 with respect to time yield equation 2, which describes the steady state transdermal flux. When the steady state line is extrapolated to time axis, the value of lag time, \( t_L \), is obtained by the intercept at \( Q = 0 \).

\[ t_L = \frac{h^2}{6D} \]  
(Equation 5)

The intercept, \( t_L \), is a measure of the time it takes for the penetrant to achieve a constant concentration gradient across the skin (Banga, 1998).

1.2.3 FACTORS AFFECTING PERMEATION

Various factors influencing absorption of penetrants through skin membrane in the in vitro and in vivo studies are discussed below:

i) Physicochemical factors

A series of studies done by a number of scientists to study the effect of physicochemical properties of the penetrant molecules on transdermal permeation are available now for reference. Important physicochemical properties that affect the permeation of drugs through the skin are discussed below;
a) **Lipophilicity**

Drug possessing both lipid and water solubility are favorably absorbed through the skin. The lipophilicity can be expressed by $n_{\text{octanol/water}}$ partition coefficient. The partition coefficient is calculated according to the following equation

$$\text{Partition coefficient} = \frac{\text{Concentration in octanol}}{\text{Concentration in aqueous phase}}$$

A penetrant having a log (octanol-water partition coefficient) ($P$) $\leq 1$ is considered as hydrophilic and penetrant having a log (octanol-water partition coefficient) ($P$) $\geq 3$ is considered as lipophilic. It has been established that the log $P_{\text{octanol}}$ is a measure to predict the partitioning of solutes from water into the SC, as skin-water partition coefficient shows high correlation with $n_{\text{octanol-water}}$ partition. This has been expressed by the equation (Mandal, 1993).

$$\log P_m = (0.51 \pm 0.06) \log P_{\text{oct}} + 0.10 (\pm 0.14) \quad \text{(Equation 6)}$$

Where $n = 22$ and $r = 0.971$

Highly lipophilic drugs get partitioned mainly into the lipid phase of the skin structure whereas hydrophilic drugs mostly are partitioned into the protein part of the skin during permeation through the skin. Therefore, a compound of optimum hydrophilic and lipophilic nature can permeate through the skin. It has been shown that the molecules having a $P_{\text{octanol-water}}$ value nearer to one can permeate easily through the skin.

The change of $P_{\text{octanol-water}}$ value of penetrant can largely influence the permeation rate, therefore changing the $P_{\text{octanol-water}}$ value by developing some derivatives of the penetrant can regulate the permeation rate of a penetrant molecule. An empirical relationship between permeability coefficient ($K_p$) and two characteristics of the permeant i.e., octanol-water partition coefficient ($P_{o/w}$) and the molecular weight (MW) was also proposed (Guy and Hadgraft, 2003).

$$\log K_p = -2.72 + 0.71 \log P_{o/w} -0.0061 \text{ MW} \quad \text{(Equation 7)}$$

b) **Hydrogen bond donor acidity ($\alpha$)**

Penetrants with high hydrogen bond donor acidity i.e., which can easily donate $H^+$ and can provide free bonds to accept hydrogen are not able to pass through the intercellular routes of SC easily. In the intercellular route, the penetrant are required to partition twice only, once at the entry and the other at the point of exit, whereas in case of transcellular route, the drug need to partition a number of times. Therefore, $P_{\text{octanol-water}}$
value is not important in intercellular routes as in transcellular route. The $P_{\text{octanol-heptane}}$ value is a measure of the hydrogen bond donor acidity and it showed a good correlation with the permeation rate of many penetrants (Mandal, 1993). This has been expressed by the equation.

$$\log P_{\text{octanol-heptane}} = (3.54 \pm 0.36) \alpha + 0.37 (\pm 0.015)$$

(Equation 8)

c) Molecular characteristics of permeant

An inverse relationship appears to exist between the absorption rate and molecular weight (MW). Small molecules permeate more rapidly than large molecules, but within a narrow range of molecular size there is little correlation between size and permeation rate, in that case lipophilicity and dissociation of the drug plays an important role. However, a correlation between diffusivity of chemical entity through membrane with the molecular size also exists

$$\log D = -S_v \log V + K_v = -S_m \log M_w + K_M$$

(Equation 9)

Where $D$ is the diffusivity, $V$ is the molecular volume, $M_w$ is the molecular weight and $S_v$, $S_m$, $K_M$ and $K_v$ are constants in a particular medium.

d) Solubility characteristics of permeants

Concentration of the drug at the absorption site influences its skin permeability. Ideally a transdermal candidate should have both aqueous as well as lipid solubility. An octanol-water partition coefficient is used as an indicator of its property. Katz and shaikh (1965), utilizing the vasoconstriction end-point for topical corticosteroids, have shown that the efficiency of percutaneous absorption may be a function of the product of the partition coefficient and the square root of the aqueous solubility.

ii) Physiological and pathological factors

Physiologic and pathologic factors also influence the permeation of the drugs through the skin and the various factors are

a) Condition of skin

The prime factor in preventing permeation through skin is the intact skin. If the skin is in abnormal state the limitations placed on the penetration do not apply. Agents such as mustard gas, acids, alkalis, etc., which injure the skin, increases its permeability.

b) Skin diseases

Defective horny layer such as skin exhibiting psoriasis and eczema usually give
an increased percutaneous absorption. Psoriasis and eczema are characterized by a virtual absence of the granular layer in the viable epidermis. In psoriasis, the proliferation is excessive whereas the keratinisation is incomplete. However, in diseased skin the degree of barrier efficiency may vary widely and depends on the precise pathological conditions of the SC. This explains why topical preparations are more effective during the early, acute phases of these diseases, and healing becomes slow when the barrier function recovers.

c) Skin age

Absorption through skin of infants is considered to be more rapid than the adult skin. This may be due to dermal atrophy and gross epidermal changes with increasing age. Changes that occur in aging skin include a) increased SC dryness, b) reduction in sebaceous gland activity resulting in a decrease in the amount of skin surface lipids c) flattening of the dermal-epidermal junction and d) atrophy of the skin capillary network resulting in a gradual attenuation of blood supply to the viable epidermis. Some studies have shown that the barrier function of the skin in vivo increases with increasing chronological age. It seems that relatively hydrophilic compounds are particularly sensitive. However, relatively little is known about the influence of such age-related changes on percutaneous absorption (Roskos et al., 1989).

d) Blood flow

Increase in blood flow causes an increase in rate of transport. Higher concentration gradient is established between the skin and dermal tissues when the blood flow is high. The normal flow rate in skin is approximately 5 ml min\(^{-1}\) /100 g tissue\(^{-1}\).

e) Regional skin sites

Percutaneous absorption varies in different anatomical regions. The differences in permeation rates may depend largely on differing thickness of the barrier layer though some investigators felt that thickness is not a determining factor in skin permeability. However according to Fick’s first law of passive diffusion, there is an inverse relationship of thickness with the penetration rate.

f) Species variation

Humans and animals display wide differences in physical skin characteristics such as the number of appendageal openings per unit area and thickness of the SC. These
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physical and structural differences affect the resistance of penetration. The skin of common laboratory rodents is more permeable than human skin. The average permeability order is rabbit > rat > guinea pig > man (Ritschel and Hussain, 1988). However, variation in this order may be found with specific substances.

g) Metabolism

The skin is a metabolically active organ and contains enzymes which are able to catalyze not only endogenous chemicals such as hormones, steroids and inflammatory mediatory but also xenobiotics including drugs, pesticides, industrial and environmental chemicals. The metabolism of xenobiotic compounds in the skin is mainly intended to detoxify potentially reactive chemicals, by converting lipophilic compounds into polar, water-soluble compounds, which are readily excreted into the bile and urine. Hence the skin is considered as a site of extra hepatic metabolism of foreign compounds (Coomes et al., 1983). An investigation on the effects of non ionic surfactants, pH and inhibitors on the metabolism and permeation of amino acids, dipeptides and pentapeptides through hairless mouse skin showed proteolytic enzyme activity and the co administration of inhibitors, permeation enhancers and pH adjustment had increased the transdermal flux significantly (Singh and Singh, 1993).

iii) Other Factors

a) Hydration

Hydration usually increases the permeability of substances. Artificially hydration can be brought by the application of an occlusive vehicle or covering of the surface. Water-soluble substances in the superficial barrier forming the natural moisturizing factor (NMF) are responsible for the hydration of the skin. Upon hydration, permeability increases four to five times (Ritschel and Hussain, 1988). Under hydration, there is an increase in the size of the pores, which results in increase in both the diffusion coefficient and activity coefficients of the permeating agent. On the other hand, dehydration also enhances absorption by causing damage to the physical structure of the barrier. When the water content of the SC falls below 10 % the layer becomes brittle and develops cracks in skin that may result improper permeation.

b) Temperature

Higher temperatures can increase penetration in two ways: (1) by increasing the
rate of diffusion of any substance in contact with skin surface by increasing molecular motion, and (2) by inducing vasodilatation of skin vessels. The rate may also increase due to a lowering of the viscosity of sebum which would facilitate its mixing with the applied preparation. The diffusion coefficient of a drug is inversely proportional to the viscosity and hence temperature is a factor influencing diffusion of a penetrant through the skin (*in vitro* and *in vivo* study).

c) **Drug concentration**

According to the Fick’s first law, the concentration gradient of the permeant between the donor and receptor fluid is the driving force of mass transfer. Drug flux will be proportional to the concentration gradient, if the membrane remains unaffected by the concentrated solutions.

d) **Effect of pH**

The pH of the vehicle affects the degree of ionization of the electrolytes. Nonionized moiety has higher acceptance to the SC, it usually shows greater passive permeability. However, permeation rates are not necessarily proportional to the concentration of the nonionized drug in the vehicle.

e) **Effect of vehicle/solvent**

The literature on influence of vehicle on skin permeation is confusing and contradictory. The primary requirement for topical therapy is that a drug incorporated in a vehicle reaches the skin surface at an adequate rate and in significant amounts. The partition coefficient between vehicle and SC affects the drug release to the underlined tissues. Hence the solubility of the drug in the vehicle is a paramount importance and manipulable factor. Other drug-vehicle factors that are important are the particle size of suspended drugs and viscosity of vehicle. Solutes held firmly by the vehicle (drug in soluble complex with the vehicle). Vehicle of dosage form in the donor cell and solvent of eluting medium also plays important role in *in vitro* study.

f) **Sorption promoters**

One method that is frequently used to increase the rate of absorption is adding materials that can combine with or dissolve barrier layers of the skin. The mechanism lies in the swelling of keratin that distorts the structure of the SC and reduces the diffusional resistance to increase the permeability. The various agents used as sorption promoters
include the hydrophilic solvent propylene glycol, surfactants, aprotic materials such as urea, dimethyl sulfoxide (DMSO), dimethyl formamide, dimethyl acetamide etc.

**g) Surfactants**

Surfactants can reduce the interfacial tension. It can emulsify the sebum, which forms a barrier to any agent, therefore increase the absorption. In skin they are supposed to cause hydration. Among the surfactants, anionic surface active agents show the best effect, followed by nonionics and cationics. Among anionic substances, the laurate ion has greater permeation. The permeability constant versus time plot for an anionic, cationic and soap was found to be nonlinear, implying that the barrier to those surfactants is being altered by the surfactants themselves as they diffuse through the skin (Ritschel and Hussain, 1988).

Nonionic surfactants have little effect in promoting skin permeation and the extent depends on the configuration of the surfactant molecule rather than the hydrophilic-lipophilic balance or surface activity. When the surfactant has several long hydrophilic chains (i.e., five or more ethylene oxide units) rather than a single or several short ethylene oxide units) rather than a single or several short ethylene oxide chains, drug absorption is increased. Some surfactants are harmful to skin.

**h) Agitation**

Agitation plays an important role during *in vitro* studies in diffusion cell. The drug diffusion through the skin occurs by eddy diffusion. Since diffusion of drug through the skin membrane follows Fick’s first law that clearly states its dependence on concentration gradient. A higher concentration near the membrane in the receptor fluid causes less permeation rate. Hence the concentration in the receptor cell should be uniform. As agitation causes uniform mass distribution and heat distribution, to maintain the uniform concentration it is essential to have an optimized agitation.

In *in vitro* experiments, it is essential to maintain uniform temperature because the diffusion coefficient is temperature dependent. This can be achieved by agitating the receptor fluid by a magnetic stirrer with optimized r.p.m (Chien, 1987).
1.3 DIFFERENT APPROACHES TO ENHANCE DRUG DELIVERY THROUGH SKIN

The intrinsic skin permeability of most drugs is inadequate to meet the therapeutic demand. Since novel technologies have been investigated to enhance the permeation rate, discussed below are the major.

1.3.1 PRODRUGS

The structural modification to get a better permeability is also a useful approach. The concept of prodrug was first introduced by Albert in 1951. It involves the chemical modification of a known pharmacologically active compound into a bioreversible form, with the aim of changing its pharmaceutical and/ or pharmacokinetic character and thereby enhancing its delivery, efficacy and therapeutic value. The particular combination of functional groups introduced into the parent drug to give the prodrug composes the promoiety. The combination of the two functional group results in the formation of a new functional group, which usually exhibits quite different physicochemical properties compared to its functional groups, but which must be capable of reverting to those components in vivo. Many types of bioreversible derivatives have been exploited to obtain prodrugs of many different drug molecules in the last decade. Table 1 shows the list of various prodrugs that has been studied for their transdermal delivery through different techniques and models.

**Table 1: Prodrugs for transdermal delivery**

<table>
<thead>
<tr>
<th>Prodrugs</th>
<th>Model</th>
<th>Technique</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>Porcine skin</td>
<td>Passive</td>
<td>Gary et al., 2006</td>
</tr>
<tr>
<td>Nalbuphine benzoate, sebacoyl dinalbuphine</td>
<td>Hairless mouse skin</td>
<td>Iontophoresis, Electrotoporation</td>
<td>Huang et al, 2005</td>
</tr>
<tr>
<td>Ketorolac amide</td>
<td>Rat skin</td>
<td>Passive permeation</td>
<td>Kim et al, 2005</td>
</tr>
<tr>
<td>3-O-alkyl ester and carbonate of Naltrexone</td>
<td>Human skin</td>
<td>Passive permeation</td>
<td>Vaddi et al., 2005</td>
</tr>
<tr>
<td>3-O-alkyl ester and carbonate of Naltrexone</td>
<td>Hairless guinea pig skin</td>
<td>Passive permeation</td>
<td>Valiveti et al., 2005</td>
</tr>
<tr>
<td>Compound Description</td>
<td>Skin Type</td>
<td>Delivery Method</td>
<td>Reference</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>3,3’-Di-(N-cyclopropylmethyl-4,5-epoxy-14-hydroxy-morphinan-6-one-3-yl) carbonate of Naltrexone</td>
<td>Abdominal human skin</td>
<td>Passive permeation</td>
<td>Hammell et al., 2004</td>
</tr>
<tr>
<td>3-O-alkyl carbonate of Naltrexone</td>
<td>Human skin</td>
<td>Passive permeation</td>
<td>Pillai et al., 2004</td>
</tr>
<tr>
<td>6-O-acyl-2-O-α-D-glucopyranosyl-α-L-ascorbic acids 1-Alkylazacycloalkan-2-one esters of Ketoprofen</td>
<td>TESTSKIN™ LSE*</td>
<td>Passive permeation</td>
<td>Tai et al., 2004</td>
</tr>
<tr>
<td>Alkyl esters of Ketorolac</td>
<td>Rat skin</td>
<td>Passive permeation</td>
<td>Doh et al., 2003</td>
</tr>
<tr>
<td>Alkylcarbonyloxymethyl of 5-fluorouracil and 6-mercaptopurine</td>
<td>Hairless mouse skin</td>
<td>Passive permeation</td>
<td>Sloan et al., 2003</td>
</tr>
<tr>
<td>Series of Nalbuphine</td>
<td>Hairless mice skin</td>
<td>Electroporation</td>
<td>Sung et al., 2003</td>
</tr>
<tr>
<td>Propranolol palmitate and propranolol stearate</td>
<td>Rat skin (in vitro and in vivo)</td>
<td>Passive permeation</td>
<td>Namdeo and Jain, 2002</td>
</tr>
<tr>
<td>Straight-chain Naltrexone ester</td>
<td>Human skin</td>
<td>Passive permeation</td>
<td>Stinchcomb et al., 2002</td>
</tr>
<tr>
<td>Poly oxy ethylene esters of Ketoprofen, Naproxen and Diclofenac</td>
<td>Human skin (in vitro and in vivo)</td>
<td>Passive permeation</td>
<td>Bonina et al., 2001a</td>
</tr>
<tr>
<td>Oligoethylene ester derivatives of 5-iodo-2`-deoxyuridine</td>
<td>Excised human skin</td>
<td>Passive permeation</td>
<td>Bonina et al., 2001b</td>
</tr>
<tr>
<td>Morpholinyl and piperazinylalkyl esters of Naproxen 5-fluorouracil, theophylline, and 6-mercaptopurine prodrugs</td>
<td>Human skin</td>
<td>Passive permeation</td>
<td>Rautio et al., 2000</td>
</tr>
<tr>
<td>Nalbuphine pivalate, enanthate and decanoate</td>
<td>Hairless mice skin</td>
<td>Iontophoresis</td>
<td>Sung et al., 2000</td>
</tr>
<tr>
<td>Amine and quaternary ammonium salt of Dehydroepiandrosterone</td>
<td>Excised rabbit skin</td>
<td>Iontophoresis</td>
<td>Laneri et al., 1999</td>
</tr>
<tr>
<td>Diacyl glyceryl ester prodrugs of Naproxen</td>
<td>Hairless mouse skin</td>
<td>Passive permeation</td>
<td>Thorsteinsson et al., 1999</td>
</tr>
</tbody>
</table>
### Introduction

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Skin Type</th>
<th>Method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esters of propranolol</td>
<td>Rat skin</td>
<td>Passive permeation</td>
<td>Udata et al., 1999</td>
</tr>
<tr>
<td>Gestodene esters</td>
<td>Hairless mouse skin</td>
<td>Passive permeation</td>
<td>Lipp et al., 1998</td>
</tr>
<tr>
<td>Acyloxyalkyl esters of ketoprofen and Naproxen</td>
<td>Human skin</td>
<td>Passive permeation</td>
<td>Rautio et al., 1998</td>
</tr>
<tr>
<td>Esters of Prednisolone</td>
<td>Hairless mouse skin</td>
<td>Passive permeation</td>
<td>Hikima and Tojo, 1997</td>
</tr>
<tr>
<td>1-alkylcarbonyl 5-fluorouracil</td>
<td>Hairless mouse skin</td>
<td>Passive permeation</td>
<td>Patrick et al., 1997</td>
</tr>
<tr>
<td>Esters of propranolol</td>
<td>Hairless mouse skin</td>
<td>Passive permeation</td>
<td>Ahmed et al., 1996</td>
</tr>
<tr>
<td>1-alkylcarbonyl of 5-fluorouracil</td>
<td>Hairless mouse skin</td>
<td>Passive permeation</td>
<td>Beall and Sloan, 1996</td>
</tr>
<tr>
<td>Alkyl ester of Buprenorphine</td>
<td>Hairless mouse skin</td>
<td>Passive permeation</td>
<td>Imoto et al., 1996</td>
</tr>
<tr>
<td>3-alkyl esters of Buprenorphine</td>
<td>Human skin</td>
<td>Passive permeation</td>
<td>Stinchomb et al., 1996</td>
</tr>
<tr>
<td>17-O-acyl Testosterone</td>
<td>Hairless rat skin</td>
<td>Passive permeation</td>
<td>Tamura et al., 1996</td>
</tr>
<tr>
<td>Indomethacin esters</td>
<td>Human cadaver skin</td>
<td>Passive permeation</td>
<td>Jona et al., 1995</td>
</tr>
</tbody>
</table>

*A human living skin equivalent model suitable for the percutaneous absorption test, TESTSKIN™ LSE-high was used.

Each individual drug presents a new challenge. Optimization of the delivery is a priority for every therapeutic molecule, both new and old. The important parameters, which influence the activity of prodrugs, are physicochemical properties, biopharmaceutics and pharmacokinetics properties, as well as the toxicity and bioactivity. The skin is a highly active metabolic organ. It contains a multitude of different enzymes that may metabolize a wide range of synthetic and naturally occurring xenobiotics. This capacity of skin is utilized by the prodrugs to revert back the active parent drug, once they are in the viable layers of the skin. Usually hydrophilic drugs diffuse poorly through the skin. Development of derivatives with higher lipophilicity usually helps in the permeation (Sloan, 1992).
Prodrug approach can be used in topical formulation (corticosteroids) as well as in the transdermal formulation, where the objective is the systemic transport of drugs (anti hypertensive agents). Though the water content of the SC is low, it is significantly higher in viable layer. Hence a good aqueous solubility is a primary requirement of the prodrugs. On the other hand high lipid solubility i.e., higher octanol – water partition coefficients, favors the passage through the SC. Small molecules (100-400 Da) permeates the skin better. But the wide distribution indicates these parameters play a secondary role to that of solubility and partition coefficient. Historically prodrug approach was used to develop derivatives resistant to hepatic metabolism, but recently approach has been attempted to develop derivatives of higher skin permeabilities. The recent investigation also shown, shapes of the molecules also play a role. Studies on cis- and trans- isomers of 11-octadecenoic acid had shown that the cis-form was able to enhance significantly the flux of salicylic acid across porcine epidermis whereas tran-isomers did not (Sloan, 1992).

**i) Physicochemical parameters**

The key parameters which control the penetration kinetics of chemicals across the skin, are the oil-water partition coefficient, lipid solubility and aqueous solubility, molecular size and shape and polarity and charge (Sloan, 1992).

*a) Oil-water partition coefficient*

It is generally accepted that the oil-water partitioning characteristics of a chemical are crucial to its ability to penetrate the skin. Over 35 years ago, it was stated that molecules with well balanced partitioning behavior were expected to transport across the skin most effectively. Increasing the lipid solubility of the promoieties almost always results in enhanced transdermal delivery of the parent drug. However, the maximum transport additionally requires water solubility also. The α- acyloxyalkyl series was used as an example. As the acyl chain length increased, the water solubility decreased, where as the lipid solubility and the partition coefficient increased. No significant differences in the rate of transdermal delivery of the parent drug by the first few members of the series of prodrugs were observed, but then the rate decreased with increasing lipophilicity. Thus, merely increasing the lipophilicity of the drug by the transient masking of a polar functional group is not sufficient to maximize percutaneous transport of the parent drug. As discussed, it is reasonable to anticipate that lipid solubility is an important factor for
percutaneous absorption. However, because the epidermal layers beneath the SC are aqueous in nature, it follows that a penetrant must also exhibit measurable water solubility in order to permeate through to the dermal microcirculation.

*b) Solubility and solubility parameters*

Determination of a suitable partition coefficient for a potential prodrug does not guarantee optimum penetration characteristics. The oil-water partition coefficient (Po/w) is the ratio of the saturation solubility of the prodrug in oil to the saturation solubility of the prodrug in water. A Po/w value of two can also be exhibited by a molecule which is very insoluble in both oil and water. It follows that such a compound will be capable of developing only a very small driving force across the skin and will penetrate rather slowly. The solubility parameter may give an indication of compounds which are likely to dissolve well in the SC lipids.

A simple approach to address this issue is to use a standard thermodynamic relationship to relate lipid solubility to melting point. A linear relationship between the steady state flux through excised human epidermis and the reciprocal of melting point has been established for an unrelated series of chemical structures (Sloan, 1992). Hence it is sensible to design prodrugs which have melting points as low as possible.

Solubility parameters provide an easy numerical method of rapidly predicting the extent of interaction between materials, particularly liquids and polymers. There is a linear correlation between the logarithm of the skin permeation of drugs and the exchange cohesive energy for the steroids testosterone, progesterone, hydrocortisone acetate, corticosterone, cortisone and dexamethasone.

*c) Molecular dimensions*

There is an ongoing debate concerning the importance of molecular weight, and hence size, on the percutaneous penetration process. Most of the skin absorption literature relates to the permeation of chemicals whose molecular weights are in the range of 100 – 400 Dalton. This four fold spread in MW is relatively small compared to the very broad span of oil-water partition coefficients and lipid solubilities exhibited by this same group of compounds. For this reason, for prodrug design it is believed that molecular weight is likely to involve a second order effect compared to partitioning and solubility.
Introduction

**d) Polarity and charge**

As stated earlier, polar molecules are poor penetrants through the lipophilic SC. Therefore, prodrug design should minimize the presence of very polar substituents (e.g. hydroxyl and amine groups).

Given the considerable resistance that the SC presents to the penetration of polar compounds, it is obvious that the skin is extremely impermeable to charged species. Presently, however there is renewed and intense interest in the use of iontophoresis as a percutaneous enhancement technique. The possibility exists, therefore, for the development of a strategy of prodrug design that would be based upon the synthesis of a charged precursor of an active drug to be delivered by iontophoresis.

**ii) Prodrug design to enhance percutaneous absorption**

With knowledge of the mechanism of skin permeation and of the major physicochemical factors which influence the kinetics of drug transport, it is possible to identify two approaches that may prove useful in the design of prodrug candidates for topical administration (Sloan, 1992).

First approach is to deduce the mechanism of penetration enhancers action on the rate limiting barrier of the SC using biophysical techniques. For example, a typical approach would involve the assessment of an enhancer’s effect on the skin penetration of a selection of drugs of different physicochemical properties. If, for instance, the enhancer was found to increase the flux of polar compounds more than that of lipophilic species, then it may be concluded that the enhancer acts specifically on the polar route through the SC.

Second approach is based on the physicochemical influences (partitioning and solubility of the penetrant) on percutaneous penetration. Therefore one can envisage that a prodrug synthesized with improved partitioning and solubility features should demonstrate enhanced permeation properties. In recent analyses of the physicochemical aspects of percutaneous penetration and its enhancement, it was revealed that (a) the solubility of the permeant in the SC should be maximized in order that the maximum transdermal flux be achieved, and (b) the promotion of lipophilic drug penetration may be most significantly affected by an agent which could facilitate the SC-to-viable epidermis transfer of the penetrant. To exemplify a prodrug design strategy that can address both
these points, if a hypothetical molecule is considered which consists of a polar parent drug, such as one containing a carboxylic acid functional group, esterified with propylene glycol, the following are the expected benefits:

(i) Esterification of carboxylic acid functional group with one of the hydroxyl group of propylene glycol prevents ionization of the polar functional group at pH values above the pKa, which might be expected to be about 4.

(ii) Propylene glycol is a common constituent of topical drug formulations. It is an excellent co-solvent and a useful solubilizing agent for drugs of low water solubility. It appears to penetrate the human skin rapidly, and it has been suggested to be capable of pulling the drug along through the SC.

(iii) Upon reaching the viable epidermis, we expect rapid hydrolysis of the propylene glycol ester prodrug by non-specific esterases, which are present in higher concentrations. This should release propylene glycol, which will then be available to enhance the solubilization of the parent drug molecules in the viable tissue

iii) Functional group consideration

Most prodrugs can be divided into two general types. The first general type is one in which one of the functional groups that gives the promoiety its characteristic physicochemical and biological properties is directly attached to the functional group in the parent drug that is to be functional group in the parent drug that is to be transiently masked. The second general type of prodrug is one in which that functional group in the moiety is separated from the functional group in the parent drug by a methylene group or vinylogous methylene group (Sloan, 1992).

For the first type of prodrug, the point of attachment of the functional group in the promoiety to the parent drug is through a heteroatom such as nitrogen, oxygen or sulphur. The heteroatom is a part of the functional group in the parent drug that is to be masked. The combination of the two functional groups is the enabling functional group. If we represent, X as the functional group and associated heteroatom from the parent drug and R as the promoiety which contains the functional groups that are responsible for the change in the properties of Drug –XH: the parent drug. Then prodrug can be represented as Drug-X-R
Table 1: Drug -XH functional groups and promoieties

<table>
<thead>
<tr>
<th>Drug -XH functional groups</th>
<th>Promoieties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-NH (Secondary amine)</td>
<td>-CH$_2$-R’ (Alkyl)</td>
</tr>
<tr>
<td>Drug-NH$_2$ (Primary amine)</td>
<td>-CH=CH-R’ (Alkenyl)</td>
</tr>
<tr>
<td>Drug-SH (Thiol)</td>
<td>-(C=O)-R’ (Alkyl carbonyl)</td>
</tr>
<tr>
<td>Drug-OH (Hydroxy)</td>
<td>-(C=O)-OR’ (Alkoxyl carbonyl)</td>
</tr>
<tr>
<td>Drug-C=O (Carbonyl)</td>
<td>-(C=O)-NR$_2$’ (Dialkyl aminocarbonyl)</td>
</tr>
<tr>
<td>Drug-(C=O)-OH (Carbonyl hydroxy)</td>
<td>-(C=O)-SR’ (Alkyl thiocarbonyl)</td>
</tr>
<tr>
<td>Drug-(C=O)-NH$_2$ (Carbonyl amine)</td>
<td>-S-R’ (Alkyl sulfenyl)</td>
</tr>
<tr>
<td>Drug-(C=O)$_2$-NH (Dicarbonyl imide)</td>
<td>-S(O)=O-R’ (Alkyl sulfinyl)</td>
</tr>
<tr>
<td>Drug-(O=S=O)-NH$_2$ (Sulfonylamine)</td>
<td>-(O=S=O)-R’ (Alkyl sulfonyle)</td>
</tr>
</tbody>
</table>

Given above (Table 1) are examples of the XH functional groups in the parent drugs that have been the object of transient modification to enhance the topical delivery of drugs containing those functional groups and some promoieties.

Table 2: Drug –X]-[R combinations

<table>
<thead>
<tr>
<th>Drug-XH</th>
<th>Structure</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-NH</td>
<td>Drug-N]-[R’</td>
<td>Alkyl amine</td>
</tr>
<tr>
<td>Drug-NH</td>
<td>Drug-N]-[(C=O)-R’</td>
<td>Alkylcarbonylamino</td>
</tr>
<tr>
<td>Drug-NH</td>
<td>Drug-N]-[(C=O)-OR’</td>
<td>Alkoxycarbonylamino</td>
</tr>
<tr>
<td>Drug-NH</td>
<td>Drug-N]-[(C=O)-NR$_2$’</td>
<td>Di alkylaminocarbonylamino</td>
</tr>
<tr>
<td>Drug-NH</td>
<td>Drug-N]-[(C=O)-SR’</td>
<td>Alkylthiocarbonylamino</td>
</tr>
<tr>
<td>Drug-NH</td>
<td>Drug-N]-[(O=S=O)-R’</td>
<td>Alkylsulfonylamino</td>
</tr>
<tr>
<td>Drug-OH</td>
<td>Drug-O]-[R’</td>
<td>Alkyl ether</td>
</tr>
<tr>
<td>Drug-OH</td>
<td>Drug-O]-[R’(C=O)-R’</td>
<td>Alkylcarbonyloxy</td>
</tr>
<tr>
<td>Drug-OH</td>
<td>Drug-O]-[R’(C=O)-OR’</td>
<td>Alkoxycarbonyloxy</td>
</tr>
<tr>
<td>Drug-OH</td>
<td>Drug-O]-[R’(C=O)-NR$_2$’</td>
<td>Dialkylaminocarbonyloxy</td>
</tr>
<tr>
<td>Drug-OH</td>
<td>Drug-O]-[R’(C=O)-SR’</td>
<td>Alkylthiocarbonyloxy</td>
</tr>
<tr>
<td>Drug-OH</td>
<td>Drug-O]-[R’ (O=S=O)-R’</td>
<td>Alkylsulfonyloxy</td>
</tr>
</tbody>
</table>
vinyllogous methylene group through a heteroatom such as NR’, oxygen, or sulphur. If X and R have the same definition as before, but now Z can be NR’, oxygen, or sulphur. This ensures that the promoiety is enzymatically or chemically labile due to the chemically labile nature of Drug-X-CH$_2$-ZH after R has been chemically or enzymatically removed.

This second type of prodrug is a soft alkyl derivative. It also increases the types of functional groups that can be introduced into a promoiety for use in combination with any specific functional group in the parent drug to serve as the enabling functional groups. Table 2 gives some examples of the Drug –X]-[R combinations (Sloan, 1992).

1.3.2 IONTOPHORESIS

The idea of transmitting therapeutic agents by means of electrical current has a history of more than 250 years. The first suggestions for the use of electricity for drug transport to be reported in the literature date from the mid-18th century and not all of them seem to be reliable. In a publication dated 1747, the Italian librarian Giovanni Francesco Pivati reports that the smell of Peruvian balsam hermetically sealed in a glass cylinder became apparent in the room after applying electrical current and could even be transmitted to another room by wire. The Turin anatomist Giovanni Battista Bianchi observed that purgatives held in the hand of a person during electrification had the same laxative effect as when administered orally. However, the data observations were of theoretical interest. The first studies using in vivo iontophoretic transport were published around the turn of the last century, when Leduc successfully demonstrated the iontophoretic delivery of strychnine and cyanide into rabbits (Cross and Roberts, 2004).

The use of electricity in the transdermal delivery was revived some twenty years ago when it was thought that the technique could be useful for the systemic delivery of macromolecules (Delgado-Charro and Guy, 2001).

Iontophoresis involves application of low intensity electric current (usually 0.5 mA/cm$^2$). The electrode was placed in a drug reservoir to the surface of the skin. A repulsion effect was developed between the electrode and the charged drug moiety, which drives the skin. Positive charge drug is delivered from anode while the negative charged drugs from the cathode (Fig. 3). The technique offers number of advantages like, the benefits of bypassing hepatic first pass effect, higher patient compliance, delivery of
ionized and unionized drugs, enabling continuous or pulsatile delivery of drug, permitting
easier termination of drug delivery, offering better control over the amount of drug
delivered, restoration of the skin barrier function without producing severe skin irritation,
improving the delivery of polar molecules as well as high MW compounds, ability to be
used for systemic delivery or local (topical) delivery of drugs and reducing considerably
the inter and intra-individual variability (Wang et al., 2005).

Figure 3: Diagram of iontophoretic technique: as current is applied the drug molecule
\((C^+)\) are repelled into skin and to the systemic circulation.

**i) Iontophoretic system**

An iontophoretic drug delivery system has three basic components: the source of
electric current, which usually consists of a battery and control electronics; an active
reservoir system, which contains the ionic therapeutic agent; and an indifferent or return
reservoir system, which contains an electrolyte and serves to complete the electric circuit.
When the active and indifferent reservoir systems are placed on the skin, the current
source causes electronic current to flow to the active reservoir where the electronic
current is transformed to ionic current. The ionic current flows through the active
reservoir, through the skin, beneath the skin towards the indifferent reservoir, and back
through the skin into the indifferent reservoir. At the indifferent reservoir, it is
transformed back into electronic current completing the circuit at the opposite pole of the
current source (Sage, 1993).
ii) Current induced drug transport

The increased flux during iontophoresis would include, flux due to the electrochemical potential gradient across the skin, change in the skin permeability due to the electric field applied and electro-osmotic water flow and the resultant solvent drag.

\[ J_{\text{ionto}} = J_{\text{electric}} + J_{\text{passive}} + J_{\text{convective}} \]  

(Equation 10)

Where \( J_{\text{electric}} \) is the flux due to electric current application, \( J_{\text{passive}} \) is the flux due to passive delivery through the skin, and \( J_{\text{convective}} \) is the flux due to convective transport due to electroosmosis (Wang et al., 2005).

iii) Pathways of iontophoresis

Skin appendages, which include sweat glands and hair follicles, are postulated to be involved in the major pathways of drug transport during iontophoresis. Other pathways, which have been shown to be involved in iontophoretic drug delivery, include paracellular transport especially for water and uncharged polar solutes, artificial shunts due to temporary disruption of the organized structure of the SC and potential-dependent pore formation (Wang et al., 2005).

iv) Mechanism of iontophoretic delivery route

Skin membrane consists of lipids (15-20%), proteins (40%) and approximately 40% water. When the drug is applied across the skin, as in case of iontophoretic treatment, an electric potential may alter the molecular arrangement of these skin components. This alteration causes some changes in the skin permeability. The “flip-flop gating mechanism” becomes an operating model for the voltage dependent pore formation in the SC which is rich in keratin, an alpha helical polypeptide. The flip-flop of polypeptide helices may occur to form a parallel arrangement. Pores are thus opened up as a result of the repulsion between neighbouring dipoles, and water molecules and ions will flow in the pore channel to neutralize the dipole moments. The phenomenon leads to an enhancement in skin permeability for peptide and protein molecules, and other charged molecules.

The isoelectric point of the skin is between 3 and 4, which is another way of saying that pores have a positive charge below pH 3 and a negative charge above pH 4 and cation permselective. Because of this original negative charge in the superficial skin layers, it is relatively easy to introduce basic drugs through the skin, which are positive in
charge. Electroosmotic flow, the transport of liquid water as a whole when an electrical field is applied across the skin, produces bulk motion of solvent itself that carries ionic or neutral solutes with the solvent stream (Lin et al., 1997). Because the skin has a negative charge, electroosmotic flow will occur in the direction of the membrane charge’s counter ion flow, i.e., from the anode to cathode direction (Guy et al., 2000). Electroosmosis is highest in solutions with a low conductivity, iontophoresis, on the other hand, is greatest in fluids with a high electrolyte concentration.

v) Theoretical considerations

At steady state flux during iontophoresis, the total flux of the dug ($J_t$) can be given as the sum of passive diffusion flux ($J_{pi}$), electrical flux ($J_{ei}$) and the convective flow ($J_{ci}$)

$$J_t = J_{pi} + J_{ei} + J_{ci}$$  \hspace{1cm} \text{(Equation 11)}

The passive flux is

$$J_{pi} = -u_i C_i \frac{dC_i}{dx} = -u_i RT \frac{dC_i}{dx} \left( \frac{d\ln C_i}{dx} \right)$$  \hspace{1cm} \text{(Equation 12)}

Where $J_{pi}$ is the passive diffusional flux of the $i^{th}$ solute drug molecule, $u$ the mobility, $C$ the solute concentration in the membrane, $\mu$ the molar free energy of energy of drug in the membrane, $R$ the universal gas constant, $T$ the temperature, $\lambda$ the activity coefficient in the membrane, and $x$ is the spatial coordinate. The subscript $i$ refers to the $i^{th}$ component, taken here to be the drug.

The electrical flux is defined as follows

$$J_{ei} = -hU_i C_i Z_i F \frac{dR_i}{dx} I_D A$$  \hspace{1cm} \text{(Equation 13)}

Where, $J_{ei}$ is the electrical flux of the $i^{th}$ solute component, $Z$ is the valence of the solute molecule, $F$ is Faraday’s constant, $R$ is the resistance, $I_D$ is the current density, $A$ is the membrane surface area, and $h$ is the proportionality constant.

The convective flux is given by

$$J_{ci} = [K \left( \frac{-dP}{dx} - \rho_{ei} \frac{dR_i}{dx} I_D \right) Ah + K' I_D A ] C_i$$  \hspace{1cm} \text{(Equation 14)}

Where $J_{ci}$ is the convective flow of the solute component, $K$ is the water permeability, $P$ is the hydrostatic pressure, $\rho_{ei}$ is the electric space and $K'$ is the proportionality constant.
Thus by neglecting the pressure gradient and letting $q_{ei} = -U_i Z_i F_i$ and $q_{ci} = -K \rho_{ei}$, the relationship for the total flux of the $i^{th}$ component is obtained by substituting the respective term in Eq. 11

$$J_i = j_{pi} + (h[q_{ei} + q_{ci}] \frac{dR_i}{dx} + \Delta C_i \mu_i A)$$  \hspace{1cm} (Equation 15)

If the pH changes and/or the transport numbers change, then the relative magnitude of the electrical and convective terms for each charged species in the system will change in such a way that total current flow and the charge neutrality conditions are satisfied. The following equation was used for describing the in vitro studies using a four-compartment diffusion cell electrode;

$$E = \frac{Y}{Y_0} = \frac{(FZ\Delta V) [Rt \{exp - (FZ\Delta V/ RT - 1)\}] - 1}{2}$$  \hspace{1cm} (Equation 16)

Where, $E$ is the flux enhancement ratio, $Y$ the flux with an electric field, $Y_0$ the flux without electric field, $V$ is the potential drop, $Z$ the molecular charge, $F$ the Faraday’s constant, $R$ the gas constant, and $T$ is the absolute temperature.

**vi) Efficiency of iontophoretic drug delivery**

The total drug delivery rate from an iontophoresis system, $R$, can be divided into two components: one component, $R_0$, due to the chemical potential gradient, and the other, $R_i$, due to the electric potential gradient. Because the driving forces resulting from the chemical and electric potential gradients act simultaneously, the following expression can be written for the total delivery rate:

$$R = R_0 + R_i$$  \hspace{1cm} (Equation 17)

But, $R_i = M_w x N_i$

Where $R_i =$ Drug delivery rate due to iontophoresis, $M_w =$ Molecular weight of the drug ion, $N_i =$ Number of moles of drug ion which cross the skin per unit time during iontophoresis

$$= \frac{E_d \times I}{F}$$  \hspace{1cm} (Equation 18)

Where $E_d$ is the efficiency of drug delivery, $I$ is the current in coulombs/second, and $F$ is the Faraday’s constant.

Therefore

$$R = R_0 + M_w x N_i$$  \hspace{1cm} Or

$$= R_0 + M_w \frac{E_d \times I}{F}$$  \hspace{1cm} (Equation 19)
If the iontophoretic flux, $F_i$, is defined as the amount of drug delivered per unit time, per unit current, then the above equation becomes:

$$R = R_0 + F_i \times I$$  \hspace{1cm} (Equation 20)

Where $F_i = \frac{M_w \times E_d}{F}$

According to the above equation, the efficiency of drug delivery can be calculated from the slope of the drug delivery rate versus current.

The relationship between the drug delivery rate ($D$) and the current ($I$) is given by Faraday’s law, which may be written as follows:

$$D = \frac{I \cdot t \cdot M}{Z \cdot F}$$  \hspace{1cm} (Equation 21)

Where $t$ is the fraction of the current carried by the drug, $M$ is the molecular weight of the drug, $Z$ is the number of charges per drug molecule and $F$ is the Faraday’s constant. The quantity $t$ is generally referred to as the transference or current efficiency.

As many current carrying species are available to carry current through the skin if an electric field is placed through the skin with the cathode in the donor solution. The total current passing through the skin will be the sum of currents carried by each of these ions:

$$I = I_{M^+} + I_{DH^+} + I_{Cl^-} + I_{H^+}$$  \hspace{1cm} (Equation 22)

Where $DH^+$ is the protonated drug ion, $H^+$ are the protons in equilibrium with the drug ions, $M^+$ are the other positively charged ions present in the donor solution, such as the counter-ions for a buffer and $Cl^-$ are the chloride ions in the subcutaneous tissues which may carry current by migrating out of the skin.

The current efficiency is, therefore

$$CE = \frac{100 \cdot I_{DH^+}}{I_{M^+} + I_{DH^+} + I_{Cl^-} + I_{H^+}}$$  \hspace{1cm} (Equation 23)

From this equation it can be said that the efficiency of the iontophoretic drug delivery over the traditional way that the iontophoretic drug delivery is performed. The first technique is to use an unbuffered donor solution to minimize competition from non-drug cations. The second technique is to use weak acid salts to control the pH in the boundary layer, and here by minimize proton transport. The third one is to increase the solubility of the drug in the donor solution to maximize the drug transport. The fourth is
to modify the permselectivity of the skin to inhibit the movement of chloride ions, which again lowers the current efficiency.

To calculate the mass of drug deliverable by iontophoresis was described as:

\[ M_D = \frac{M_w \times t \times i_D}{F \times Z_D} \]  

(Equation 24)

Where \( M_D \) is the dosage of the drug, \( F \) is the Faraday’s constant, \( Z_D \) is the valence, \( M_w \) is the molecular weight, \( t \) is the time in seconds and \( i_D \) is the current carried by the drug ion. It is possible to determine the \( i_D \) experimentally, but it is also possible to express \( i_D \) in terms of iontophoresis system parameters and hence express the dosage of the drug (\( M_D \)) in terms of these same system parameters. The current efficiency for drug transport, \( E_D \), can be defined in terms of the total iontophoretic current \( I \) as:

\[ E_D = \frac{i_D}{I} = \text{current efficiency} \]  

(Equation 25)

Where \( i_D \) is the current carried by the drug ions, one of the many current carrying ions in the system.

Hence

\[ M_D = \frac{M_w \times t}{F \times \frac{i_D}{Z_D}} = \frac{M_w \times t}{F \times \frac{E_D \times I}{Z_D}} \]  

(Equation 26)

The total iontophoresis current can be written as the product of electrode area \( A \) and the current density \( I_D \). Thus

\[ M_D = E_D \times I_D \times A \times \frac{M_w \times t}{Z_D \times F} \]  

(Equation 27)

Hence this equation allows calculating the drug that can be delivered by iontophoresis (Khar and Nanda, 1997).

vii) Factors affecting iontophoresis

The technique of iontophoresis depends upon several physicochemical variables apart from factors which affect the skin uptake of drugs during passive diffusion. Current intensity, vehicle pH, type of electrode, co-ions, concentration, conductivity of drugs and skin impedance affect the transport of drugs by iontophoresis (Kalia et al., 2004).

a) Current intensity

The electromigratory contribution to iontophoretic flux is directly proportional to the applied current provided when the respective ion concentrations are kept constant. In
general, this holds true both for small molecules and peptides. Although increasing the current produces an increase in iontophoretic transport, at higher current levels a saturation level is obtained. After a limiting transport number is achieved, further increase in current has no effect.

b) \( \text{pH} \)

This affects iontophoresis in two ways. The \( \text{pH} \) of the donor solution influences the \( \text{pH} \) of the skin and thus makes the skin a permselective membrane especially if the \( \text{pH} \) of the skin rises above 4. This causes the carboxylic acid moieties in the skin to become ionized and the cationic drugs are promoted. The \( \text{pH} \) of the donor solution also affects the ionization of the drug itself. Thus a weakly basic drug will be ionized to a lower extent at \( \text{pH} \) higher than its pKa and will not permeate by electromigration in presence of iontophoresis. The drug will be more dependent on electroosmosis to travel across the skin (Wang et al., 2005).

c) \( \text{Type of electrode} \)

Type of electrodes used also affect the iontophoretic delivery. Silver-silver chloride electrodes (Ag/AgCl) are the most preferred as they resist the changes in \( \text{pH} \) which are generally seen during the use of platinum or zinc-zinc chloride electrodes. The following reactions typically occur at the anode.

\[
\text{Ag} + \text{Cl}^- \rightarrow \text{AgCl} + \text{e}^-
\]

The electron is released to the circuit and insoluble AgCl precipitates at the anode surface. In the case of other metals like platinum, the chloride ion at the anode will be converted to \( \text{Cl}_2 \), which will in turn react with water to generate hydronium ions. These then migrate to the donor solution and compete with similar-charged drug ions and being highly mobile enters the skin thus reducing drug transport and simultaneously causing skin irritation (Wang et al., 2005).

d) \( \text{Co-ion} \)

The presence of a co-ion results in competition between the drug and the co-ion. It reduces the fraction of the current available to the drug and thus causes reduction in drug flux. A most common source of co-ions is the buffer added to control the \( \text{pH} \) of the donor medium (Wang et al., 2005).
e) **Drug concentration**

Drug concentration and its impact on iontophoretic flux is one of the most commonly studied experimental parameters. It suggests the existence of a fairly straightforward correlation between the amount of drug in the formulation and the observed flux. However, the experimental results differ from the theory. Increasing the amount of drug in formulation may not increase the number of molecules in membrane; second, the concentrations and mobilities of competing ions play an important role; and third, structure and physicochemical properties of specific drugs may influence its ability to permeate through iontophoretic transdermal pathways (Kalia et al., 2004).

f) **Resistance of skin**

Under electricity, the dermal resistance decreases. However, it is desirable that once the current is removed, the skin resistivity is restored (Singh and Singh, 1993).

g) **Drug salt form**

It has been reported that different salt forms have different specific conductivities and that conductivity experiments *in vitro* will provide information concerning the general suitability of a drug for iontophoresis. The salt form of the drug must be considered along with the pH of the solution for determining the amount of drug in the ionized state (Gangarosa et al., 1978).

h) **Stability of the drug during the iontophoresis process**

The drug undergoing iontophoresis must be stable in the solution environment up to the time of iontophoresis and also during the iontophoresis process. Drugs which are easily oxidized or reduced must be appropriately formulated. This is important because oxidation or reduction of a drug not only decreases the total drug available but the degradation compounds, if they possess the same charge as the drug ion, will compete with the drug ion and reduce the overall transmembrane rate of the drug (Delago-Charro and Guy, 2001).

i) **Molecular size**

It has been shown that the permeability coefficients in positively charged, negatively charged and uncharged solutes across excised human skin are a function of molecular size. When the molecular size increases, the permeability coefficient decreases (Yoshida and Roberts, 1993). However, there are certain solutes with a relatively high
molecular size (e.g. insulin, vasopressin and several growth hormones), which have also been shown to penetrate the skin barrier into the systemic circulation.

1.3.3 OTHER APPROACHES

i) Chemical potential adjustment

The vehicle plays an important role in permeation and achieving a thermodynamic activity that favors partitioning of the drug to the skin is one of the approaches used. The mass transport through the skin is given by the following equation.

$$\frac{dm}{dt} = aD/\gamma h$$

(Equation 28)

where $dm$ is the mass of diffusant, $dt$ is the time, $a$ is the thermodynamic activity of drug in its vehicle, $D$ is the diffusion coefficient, $\gamma$ is the effective activity coefficient in the skin barrier and $h$ is the thickness of the membrane (Barry, 2001). Artificially designed supersaturated solutions are used to enhance the permeation rate (Pellet et al., 1997).

ii) Ion pairs

Charged molecules do not readily penetrate SC. One technique forms a lipophilic ion pair, by adding an oppositely charged species. The complex partitions into the SC lipids, as charges temporarily neutralize. The ion pair diffuses to the aqueous viable epidermis, there to dissociate into its charged species, which partition into the epidermis and diffuse onward (Megwa et al., 2000).

iii) Eutectic systems

The melting point of a drug influences solubility and hence skin penetration. According to regular solution theory, the lower the melting point, the greater the solubility of a material in a given solvent, including skin lipids. The melting point of a drug delivery system can be lowered by formation of a eutectic mixture: a mixture of two components which, at a certain ratio, inhibit the crystalline process of each other, such that the melting point of the two components in the mixture is less than that of each component alone. EMLA cream, a formulation consisting of a eutectic mixture of lignocaine and prilocaine applied under an occlusive film, provides effective local anesthesia for pain-free venepuncture and other procedures. The 1:1 eutectic mixture (m.p.18°C) is an oil, which is formulated as an oil-in-water emulsion thereby maximizing the thermodynamic activity of the local anesthetics. A number of eutectic systems containing a penetration enhancer as the second component has been reported, for
example: ibuprofen with terpenes, menthol and methyl nicotinate, propranolol with fatty acids; and lignocaine with menthol. In all cases, the melting point of the drug was depressed to around or below skin temperature thereby enhancing drug solubility. However, it is also likely that the interaction of the penetration enhancer with SC lipids also contributed to the increased drug flux (Benson, 2005).

iv) Liposomes and other vesicles

Liposomes are colloidal particles, typically consisting of phospholipids and cholesterol, with other possible ingredients. These lipid molecules form concentric bimolecular layers that may entrap and deliver drugs to the skin. It is a localizing effect whereby vesicles accumulate drugs in SC or other upper skin layers. Generally, liposomes are not expected to penetrate into viable skin, although occasional transport processes were reported (Barry, 2001).

v) High velocity particles

The solid particles can be directly injected to the skin using the supersonic shock wave of helium gas (e.g. PowderJect). The advantages of the system include pain-free delivery, improved efficacy and bioavailability, targeting to a specific tissue, SR, or fast release, accurate dosing, overcomes needle phobia and safety. However, there have been problems with bruising and particles bouncing off skin surfaces. Regulatory authorities will need convincing that high velocity particles smashing through the SC really do not damage to this elegant structure, which is not readily repaired, nor do they carry surface contaminants such as bacteria into viable skin layers (Barry, 2001).

vi) Chemical penetration enhancers

Substances temporarily diminishing the barrier of the skin, known also as accelerants or sorption promoters. They can enhance drug flux. Many enhancers, such as azone, DMSO, alcohols, fatty acids and terpenes, have been shown to increase permeability by disordering or ‘fluidising’ the lipid structure of the SC. In some cases the enhancers penetrate into and mix homogeneously with the lipids. However, others such as oleic acid and terpenes, particularly at high concentration, pool within the lipid domains to create permeable ‘pores’ that provides less resistance for polar molecules (Barry, 2001).
vii) Microneedle array

SC can be bypassed by injection and one development of this approach is a device of 400 microneedles, which insert drug just below the barrier (Henry et al., 1998). The solid silicon needles (coated with drug) or hollow metal needles (filled with drug solution) penetrate the horny layer without breaking it or stimulating nerves in deeper tissues. Flux increases up to 100,000-fold are claimed. The technique may also be combined with iontophoresis.

viii) Skin abrasion

The abrasion technique involves the direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medicaments. Some of these devices are based on techniques employed by dermatologists for superficial skin resurfacing, e.g. microdermabrasion. Microdermabrasion uses a stream of aluminium oxide crystals.

Adhesive tape, which removes SC prior to drug application, and a microinfusor device, has also been proposed to deliver drugs through transdermal. One the other hand a blister by suction, an epidermatome removes the raised tissue, after which a solution delivered directly to the exposed dermis (Barry, 2001).

ix) Medicated tattoos

A related means of delivering compounds transdermally has been developed by Lipper-Man Ltd. There is no predetermined duration of therapy for Med-Tats. Instead, it provides a color chart that can be compared to the color of the patient's tattoo to determine when the tattoo should be removed. This visual comparison, which relies on dyes incorporated into the patch, introduces a significant amount of inter patient variability (Bogner and Wilkosz, 2005).

x) Ultrasound (Phonophoresis, Sonophoresis)

This technique, used originally in physiotherapy and sports medicine, applies a preparation topically and massages the site with an ultrasound source. The procedure was extended to TDD studies. The ultrasonic energy (at low frequency) disturbs the lipid packing in SC by cavitation. Shock waves of collapsing vacuum cavities increase free volume space in bimolecular leaflets and thus enhance drug penetration into the tissue (Barry, 2001).
xi) Electroporation

Skin electroporation (electropermeabilization) (Prausnitz et al., 1993) creates transient aqueous pores in the lipid bilayers by application of short (micro to millisecond) electrical pulses of approximately 100–1000 V/cm. These pores provide pathways for drug penetration that travel straight through the horny layer (Jadoul et al., 1999). Significant movement can also occur between pulses by simple diffusion due to relatively persistent changes in the SC lowering its resistance. The process may also transport into the integument, vaccines, liposomes, as well as nanoparticles and microspheres. Electroporation may combine with iontophoresis to enhance the penetration of peptides such as vasopressin, neurotensin, calcitonin and luteinising hormone releasing hormone (LHRH) (Banga et al., 1999). Electroporation has also been combined with ultrasound.

xii) Magnetophoresis

Limited work probed the ability of magnetic fields to move diamagnetic materials through skin (Murthy, 1999). Langer discussed the interesting idea of employing intelligent systems based on magnetism or microchip technology to deliver drugs in controlled, pulsatile mode (Santini et al., 1999).

xiii) Laser radiation

This method involves direct and controlled exposure of a laser to the skin, which results in the ablation of the SC without significantly damaging the underlying epidermis. Removal of the SC using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs (Benson, 2005).

1.4 IN VITRO EVALUATIONS

In vitro evaluation studies are an important means of obtaining preliminary ideas about drug availability in the body. Ever since the development of dosage forms, scientists are endeavoring to develop a foolproof in vitro evaluation system which will have a high degree of correlation with data from in vivo physiological availability of a drug. Of course, it is to be kept in mind that an in vitro testing programme cannot give an absolute accurate judgment of dosage form efficacy. Although many of the condition present with the body are simulated during the in vitro experiments, the ultimate criteria governing the dosage form performance always depend on the actual conditions in vivo (Banker and Anderson, 1991). Example in carrying out the dissolution procedures in
in vitro, the peristaltic movement is sought to be maintained at an optimum rate, considering that the conditions in the GIT will be similar. But we fail to take into account the intrinsic changes occurring the GIT due to a number variation like a full stomach and empty stomach, pathophysiological conditions of the GIT etc. However, despite their limitations, these in vitro tests are still important because:

1) They can serve as a measure of quality control in order to check inter and intra batch variations of a particular product.

2) Many potential drugs and dosage forms can be preliminarily screened for bioavailability by these methods. If a dosage form fails to qualify in the in vitro evaluation itself, then there is little chance that it will display excellent dissolution and absorption characteristics in vivo.

3) An in vitro-in vivo correlation can be set up to judge the effects of formulation changes and other variables affecting dosage form performance.

4) In vitro data alone can sometimes predict which particular drug or dosage form will result in optimization of a particular property/ effect desired.

Since the pharmaceutical world has been a surge in developing controlled release formulations like TDDS, untiring efforts have been directed towards developing suitable systems to evaluate their performance. An apparatus designed for in vitro TDDS studies should be capable of determining accurately the intrinsic release rate or the permeation rate. One approach in fulfilling this goal is to reach a constant value of the drug flux by increasing the stirring rate and calculate the intrinsic release profile at that speed. But this process has its own drawback also, since highly hydrophilic drugs, highly viscous solutions etc pose problems during the studies.

It should be always remembered that since the permeation, diffusion and partition of drugs are often influenced by the hydrodynamic character of the in vitro system used, which can affect heat transfer, the flow pattern in the system must be precisely controlled. For transdermal delivery the main barrier effect is exerted by the SC. In case of an in vitro apparatus with poor mixing conditions, the rate of drug release from the TDDS may be distorted by the diffusion boundary layer. In this case, in vitro permeation rate will be very close, due to error and it will be wrongly concluded, that the rate of drug delivery is controlled by the TDDS, and not by the skin permeation. In contrast, a properly designed
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*in vitro* apparatus can ensure that the mechanism of drug delivery is solely from the TDDS (Chien, 1987).

Various types of *in vitro* evaluation apparatus for TDDS have been designed to determine the drug release and permeation profiles, among which, an apparatus designed by Scheuplin in 1965 may be considered as the first of its kind. Later in 1968, Garrett and his coworkers also developed an apparatus for *in vitro* diffusion studies. Menschel and Maibach used a modified electrolysis unit to study the process of percutaneous absorption of various drug entities. In 1975, Michaelis and coworkers designed another skin permeation cell, which had a stirring component made of Teflon and inserted through an open port and the rotation of which was controlled by a synchronous speed motor. Durrheims et al also fabricated a new diffusion cell in 1980, which consisted of a 2 compartments, donor and receptor of 1.5 ml capacity each. The impeller for stirring was accommodated through an open port, and the second open port served as a way for fluid replenishment. The common drawbacks of these apparatus were:

1) The donor and receptor compartment were open to the atmosphere, which led to evaporation of fluids, resulting in changes of concentration which severely affected the results of release and permeation profiles.

2) There was no precise control of temperature in the system. Generally both the compartments are maintained at the same temperature either by immersing it in a water bath or by retaining it on a thermostated controlled oven. This step failed to simulate the physiological conditions where the temperature of the donor and receptor compartments varies by a few degrees.

The Franz diffusion cell had been developed in 1978 was used for studying release and skin permeation profiles of the drug from TDDS. Franz diffusion cell has been marketed by crown glass company of US and has been widely used in studying the kinetics of percutaneous absorption from TDDS. This cell consists of a receptor compartment of approximately 10-12 ml and the effective area of permeation ranging from 1.57-4.71 cm². The elution media in the receptor compartment is maintained constant by a thermostatic water jacket surrounding the receptor compartment. Though this system was superior to the above mentioned systems with respect to the temperature control, still this system suffers many disadvantages related to hydrodynamics affecting
release kinetics. The thick stationary diffusion layer below the skin or TDDS reduces the rate of release of permeation. Considering these disadvantages a new diffusion cell has been designed by Chien et al, 1983 (called as Keshary Chien diffusion cell) to overcome the problems of the diffusion layer. The receptor compartment of this all has a volume of 12 ml and skin surface area of 3.14 cm$^2$. The receptor solution is stirred by a star head magnet at 600 rpm driven by synchronous motor. The major difference between the Franz and Keshary diffusion cell are as follows:

1) In the Franz cell, a thick diffusion layer existed due to its peculiar wide necked and narrow bottomed design, the uniform cylindrical pattern of the Keshary Chien cell minimized the problem.

2) In Keshary cell, use of star headed magnet appreciably reduces vortex formation in the elution media, unlike that produced by a bar magnet in the Franz diffusion cell.

3) Since in the Keshary cell, the thermostated water jacket surrounds the entire cell excepting the ports, there is an uniform maintenance of temperature through the entire volume of the elution media, in comparison to the Franz cell, where only a portion of the elution media could be thermostatically controlled.

4) The sampling port of the Franz cell is not stoppered, leading to subsequent evaporation of the elution medium. This defect was rectified in the Keshary Chien cell by providing a stopper for the sampling port.

Although the Keshary Chien cell could overcome the major drawbacks of the Franz cells, it is retained its inherent disadvantages. They are

1) In this cell, the temperature of the receptor cell is controlled thermostatically, but the donor compartment remains uncontrolled and exposed to the atmosphere. This is contrary to the human body conditions where the skin surface maintains an approximately constant temperature at 32 $^\circ$C, while the body fluids are at 37 $^\circ$C.

2) This cell being of the vertical type, does not simulate the postural condition of the body surface (where the TDDS is to be applied) unless in a sleeping position. These subsequently lead to fabrication of a horizontal type cell.

3) One more handicap of both Franz and Keshary Chien cell are that they are unsuitable for evaluating liquid systems to be used as TDDS. Keeping the disadvantage
of Keshary Chien cell in view, a new cell was developed, Valia Chien cell.

Valia Chien cell consists of two half cells, each of 3.5 ml capacity. The elution mediums in both half cells are stirred by two star magnets operated by a synchronous motor. The membrane area is very small (0.64 sq.cm). The temperature of the system can be maintained isothermally or non isothermally by the surrounding water jacket. The thermodynamics of Valia Chien cell was studied by a group of scientists. A second of this type has been also developed by Ghannan and Chien, which has been calibrated by Tojo et al. This cell is almost like the Valia Chien cell, but is greater in volume. The half cell capacities are 140-250 ml. The membrane area is 13.9cm$^2$. The stirring of elution media is by a bar magnet (2.45 cm) instead of a star magnet at a speed of 60 – 100 r.p.m. The temperature control is by a circulating thermostated water jacket (Chien, 1987).

Two compartment vertical or horizontal diffusions cells are typically used for in vitro transdermal iontophoresis. Various researchers designed or modified the existing diffusion cells. One of the designs involved three compartments separated by two pieces of skin, with both SC sides oriented towards the compartment containing an electrode, in another design, the location of return electrode was changed. It was observed that the alteration in diffusion cell configuration and/ or return electrode placement relative to the membrane had little effect on the drug transport, thus permitting the use of a simple experimental design (Singh and Singh, 1993).

Figure 4: Diagrammatic representation of Franz diffusion cell
Synthesis of prodrugs of selected antihypertensive agents and their in vitro assessment for transdermal delivery

Figure 5: Diagrammatic representation of Keshary Chien diffusion cell

Figure 6: Diagrammatic representation of Valia Chien diffusion cell
1.5 MANAGEMENT OF HYPERTENSION

Hypertension is a major health problem throughout the world because of its high prevalence and its association with increased risk of CVD. But the timely diagnosis can reduce the occurrence of major CVD. Advances in the diagnosis and treatment of hypertension, reduces coronary heart disease and stroke mortality in industrialized countries. However, in many of the industrialized countries, the control rates for high BP have actually slowed in the last few years. It is estimated that by 2010, 1.2 billion people will be suffering hypertension worldwide. In the Eastern Mediterranean Region, the prevalence of hypertension averages 26% and it affects approximately 125 million individuals. Of greater concern is that cardiovascular complications of high BP are on the increase, including the incidence of stroke, end-stage renal disease and heart failure (Khatib and El-Guindy, 2005).

Recent data suggest that individuals who are normotensive at age 55 years have a 90% lifetime risk for developing hypertension. The relationship between BP and risk of cerebrovascular disease events is continuous, consistent and independent of other risk factors. The higher the BP, the greater the chance of myocardial infarction, heart failure, stroke and kidney disease. For individuals aged 40–70 years, each increment of 20 mmHg in systolic BP or 10 mmHg in diastolic BP doubles the risk of CVD. These alarming data support a need for greater emphasis on public awareness of the problem of high BP and for an aggressive approach to antihypertensive treatment.

1.5.1 HYPERTENSION

BP is the measure of the force of the blood moving through bodies circulatory system. This complex network of veins and arteries contains blood vessels that can be as large as a banana or so narrow that blood cells can barely squeeze through them. Ideally, the blood flows through almost 100,000 miles of arteries and veins in a smooth stream, much like water flowing through a homes faucet into the sink or tub.

Within the body, the beats of heart create a pressure-driven force that sends the blood moving through the body's arterial pathways in a steady, pulsating rhythm. This force is measured to determine the BP level.

With each beat (the heart contracts), sending out a surge of pressure into the bloodstream. This surge period is called systolic from a Greek word meaning to contract.
After the pressure surge, the heart rests for a brief time and expands to get ready for another beat. The arteries that have received the surge of blood now rebound, forcing it further through the system. This is called the diastolic or expansion period. Doctors measure the BP during each of these periods. They often say, the pressure is 120 over 80 or some other combination of numbers. This first number is a measure of the systolic push of the heart beat on the blood. The second number is diastolic measurement of the pressure in arteries as blood continues to flow through the system while heart is at rest.

Finding this measurement is easy. Anyone can do it with a simple home monitoring device called a sphygmomanometer or BP cuff. The doctors device may be a little more sophisticated, with a cuff, a stethoscope, and a pressure gauge, but they all work pretty much the same way. When the pressure is measured, this cuff is tightened to cut off the circulation momentarily. The cuff is loosened, and as the blood begins to flow again, the device measures the systolic and diastolic forces. The measurement is expressed in numbers as though they were a fraction (e.g. 140/90). A detailed classification of BP levels is given below (Khatib and El-Guindy, 2005).

**Table 3: Classification of BP levels (mm Hg)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>High-normal</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
<td>160-179</td>
<td>100-109</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>≥180</td>
<td>≥110</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥140</td>
<td>&lt; 90</td>
</tr>
</tbody>
</table>

**i) Causes of High BP**

There are two types of high BP: primary (essential) hypertension and secondary hypertension. Although the exact cause of primary hypertension is not known, contributing factors include heredity, obesity, lack of exercise, diet (including salt intake), cigarette smoking, sex, race, age, and even personality. Over 90 percent of all hypertensive fall into primary category. Secondary hypertension may be linked to kidney disease, endocrine disorders, use of oral contraceptives and excessive use of alcohol.
There is some evidence that continual stress can trigger biochemical changes within the body that raise BP and keep it high. However, the common myth that nerves or a case of the jitters can bring on hypertension simply is not true. High BP is a disease, and even though often silent, must be treated promptly, exactly as directed by physician.

Changes in the arteries can complicate the problem. Normally the arteries are rather springy, in addition to expanding and contracting in rhythm with the heart, they adjust themselves to the volume of the blood and to other conditions within the body, stretching or tightening up as necessary to raise, lower, or maintain BP. Various factors like stress, diet, heredity, lifestyle and aging have a detrimental effect on arteries. They become less elastic and thus less able to adjust to changes in body and they tend to become coated with arterial cholesterol plaque, a fatty deposit that clogs them, just as deposits in a water pipe can cause a sink to back up. This condition, called arteriosclerosis can obstruct coronary arteries and can lead to a stroke if arteries that supply blood to brain become blocked. A guide to follow up for adults is shown below:

**Table 4: Guide to follow-up of adults 18 years and over**

<table>
<thead>
<tr>
<th>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 120</td>
<td>&lt; 80</td>
<td>Recheck in 2 years</td>
</tr>
<tr>
<td>120-139</td>
<td>80-89</td>
<td>Recheck in 1 year</td>
</tr>
<tr>
<td>140-159</td>
<td>90-99</td>
<td>Confirm within 2 months</td>
</tr>
<tr>
<td>160-179</td>
<td>100-109</td>
<td>Refer within 1 month</td>
</tr>
<tr>
<td>≥180</td>
<td>≥110</td>
<td>Refer within 1 week or immediately depending on clinical situation</td>
</tr>
</tbody>
</table>

**If high BP is identified early enough, right at its initiation, the first line of defense is an attempt to modify the risk factors associated with it. Of course, one cannot do anything about our heredity, age, race, or sex; but can lose weight, exercise more, stop smoking, and improve our eating habits.**

In most cases, the mainstay of treatment for hypertension is medication. It brings BP down quickly and keeps it down. And although it does not cure the disease (if one have not improved your diet and lifestyle, BP almost always shoots back up when medication is discontinued), it does prevent the serious and even life-threatening complications that can result if high BP is left untreated.
1.5.2 DRUGS USED IN THE TREATMENT OF HYPERTENSION

The first step is usually a prescription for one of five types of medication, a beta blocker, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker or a diuretic. If these drugs, either alone or in combination, fails to bring BP under control, other classes of drugs may be prescribed.

i) Beta blocker the drug of first choice

To lower BP in patients with angina pectoris a beta blocker is the drug of first choice. Although there is no evidence, it seems reasonable to use a beta blocker as first choice in patients where the drug can be used to treat more than the hypertension, e.g. patients with frequent recurrent migraine or patients with sympathetic hyperactivity, resting tachycardia, and palpitations. Beta blockers should not be used in patients with asthma or other forms of obstructive airways disease.

Beta blockers reduce high BP by throttling back the force and speed of the heart. They may also reduce BP by a direct effect on the bodies master controls, the CNS. Propranolol is the granddaddy of the beta blocker family and the first of its class to be approved by the FDA for use in US.

Beta blockers decrease morbidity and mortality in hypertensive patients

There are only two trials in which the effectiveness of beta blockers (propranolol and atenolol) can be compared with placebo. When the data from these trials are combined, there is a trend towards a reduction in the incidence of total stroke, log odds ratio, 0.77 (0.59-1.04), but little effect on total coronary events, 0.89 (0.71-1.13). The lack of effectiveness of atenolol based therapy in reducing coronary events corroborates the findings of other studies. It may be that the high cardioselectivity of atenolol is not a desirable pharmacological action.

There are three trials in which the effectiveness of beta blockers can be compared with thiazides. When the results of these trials are combined in a meta-analysis the patients receiving thiazide had a non statistically significant reduction in the incidence of stroke, 0.81 (0.58-1.14) and coronary events, 0.92 (0.74-1.14). In post myocardial infarction trials, non-selective beta blockers and high dose beta-1 selective blockers, but not oxprenolol or pindolol, beta blockers with high partial agonist (increased sympathomimetic) activity, reduce risk of reinfarction and mortality (Yusuf et al., 1985).
With the evidence presently available, physicians are advised to prescribe a non-selective beta blocker in the lowest dose required to lower the BP. The beta blockers used are given below:

**Table 5: Beta Blockers used**

<table>
<thead>
<tr>
<th>Beta Blockers</th>
<th>Trade Name</th>
<th>Usual Dosage Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propanolol</td>
<td>Inderal®</td>
<td>20-120 mg BID</td>
</tr>
<tr>
<td></td>
<td>Inderal® LA</td>
<td>60-240 mg daily</td>
</tr>
<tr>
<td>Nadolol</td>
<td>Corgard®</td>
<td>20-160 mg daily</td>
</tr>
<tr>
<td>Timolol</td>
<td>Blocadren®</td>
<td>5-20 mg BID</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Tenormin®</td>
<td>25-100 mg daily</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Betaloc®, Lopressor®, Betaloc®</td>
<td>25-100 mg BID</td>
</tr>
<tr>
<td></td>
<td>SR, Lopressor® SR</td>
<td>100-200 mg daily</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>Sectral®, Monitan®</td>
<td>100-400 mg daily</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>Trasicor®</td>
<td>20-160 mg BID</td>
</tr>
<tr>
<td></td>
<td>Slow Trasicor®</td>
<td>80-320 mg daily</td>
</tr>
<tr>
<td>Pindolol</td>
<td>Visken®</td>
<td>5-15 mg BID</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Trandate®</td>
<td>100-400 mg BID</td>
</tr>
</tbody>
</table>

**ii) ACE inhibitors**

ACE inhibitors, which include benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril, block the production of angiotensin II, a chemical the body produces to raise BP. Angiotensins normal role is to maintain equilibrium when BP drops. It acts directly on the arteries, tightening them up to raise the pressure. The ACE inhibitors can bring BP down quickly but in very rare cases can cause kidney damage or a reduction in the number of white blood cells (leading to an increased susceptibility to infection). When one of these drugs fails to reduce BP sufficiently, the doctor usually prescribe a version that includes a diuretic for extra pressure reduction.

ACE inhibitors have been clearly shown to prolong survival in patients with congestive heart failure (CHF). They are therefore the obvious first choice in patients with hypertension and CHF. It is not established at the present time whether ACE inhibitors have a unique renal protective effect in diabetic nephropathy. A recent study
suggests that ACE inhibitors increase the risk of hypoglycemia in treated diabetic patients (Herings et al., 1995). There are no proven therapeutic differences between the ACE inhibitors; drug choice can be made based on convenience and cost.

**Table 6: ACE Inhibitors used**

<table>
<thead>
<tr>
<th>ACE Inhibitors</th>
<th>Trade Name</th>
<th>Usual Dosage Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinapril</td>
<td>Accupril®</td>
<td>5-40 mg daily</td>
</tr>
<tr>
<td>Ramipril</td>
<td>Altace®</td>
<td>1.25-10 mg daily</td>
</tr>
<tr>
<td>Captopril</td>
<td>Capoten®</td>
<td>12.5-50 mg daily</td>
</tr>
<tr>
<td>Perindopril</td>
<td>Coversyl®</td>
<td>2-8 mg daily</td>
</tr>
<tr>
<td>Benazepril</td>
<td>Lotensin®</td>
<td>5-40 mg daily</td>
</tr>
<tr>
<td>Cilazapril</td>
<td>Inhibace®</td>
<td>1-10 mg daily</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Prinivil®, Zestril</td>
<td>5-40 mg daily</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Monopril®</td>
<td>10-40 mg daily</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Vasotec®</td>
<td>5-40 mg daily</td>
</tr>
</tbody>
</table>

**iii) Calcium channel blockers**

Calcium channel blockers are the most widely prescribed drugs in the US today.

**Table 7: Calcium channel blockers used**

<table>
<thead>
<tr>
<th>Calcium channel blockers</th>
<th>Trade Name</th>
<th>Usual Dosage Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td>Cardizem®</td>
<td>60-120 mg BID, TID</td>
</tr>
<tr>
<td></td>
<td>Cardizem SR®</td>
<td>60-180 mg BID</td>
</tr>
<tr>
<td></td>
<td>Cardizem CD®</td>
<td>120-300 mg daily</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Isoptin®</td>
<td>80-160 mg BID, TID</td>
</tr>
<tr>
<td></td>
<td>Isoptin SR®</td>
<td>120-240 mg BID</td>
</tr>
<tr>
<td></td>
<td>Verelan®</td>
<td>120-480 mg daily</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Adalat®</td>
<td>5-30 mg BID, TID</td>
</tr>
<tr>
<td></td>
<td>Adalat PA®</td>
<td>10-30 mg BID</td>
</tr>
<tr>
<td></td>
<td>Adalat XL®</td>
<td>30-90 mg daily</td>
</tr>
<tr>
<td>Felodipine</td>
<td>Plendil®, Renedil®</td>
<td>2.5-20 mg daily</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Norvase®</td>
<td>5-10 mg daily</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Cardene®</td>
<td>20-40 mg TID</td>
</tr>
</tbody>
</table>
Introduction

Like so many of the other drugs used for hypertension, they act by dilating the arteries and reducing resistance to the flow of blood. They have proved to be beneficial not only for high BP, but also for angina and other problems of a weakened heart. Included in this group are drugs such as are given below. Some calcium channel blockers are now available combined with an ACE inhibitor in a single pill. Among these new double treat medications are brands named Lexxel, Lotrel, and Tarka.

iv) Angiotensin II receptor antagonists

Angiotensin II receptor antagonists, a new class of drugs, work to lower BP by blocking angiotensin from binding to receptor sites in the smooth muscles of the blood vessels. This blocking action stops the angiotensin from tightening the arteries and raising the BP. Angiotensin II receptor antagonists available currently include: valsartan (Diovan), candesartan (Atacand), eprosartan (Teveten), irbesartan (Avapro), losartan potassium (Cozaar), olmesartan (Benicar), and telmisartan (Micardis). Most of these drugs are also available combined with a diuretic.

v) Diuretics

Diuretics, such as furosemide (Lasix), chlorothiazide (Diuril), hydrochlorothiazide (Esidrix, Hydrodiuril), and spironolactone (Aldactone), make it difficult for the kidneys to retain water and salt, which are then filtered out into the urine. Increasing the amount of urine reduces the amount of fluid in the bloodstream, and hence the pressure on artery walls. Because some important chemicals may be washed out along with the water and salt, a doctor may prescribe supplements, most commonly a potassium supplement to go with the diuretic.

Recently, the National Heart, Lung and Blood Institute and the National Institute on Aging in Bethesda, Maryland, warned that high doses of the fast-acting form of nifedipine (Procardia, Adalat), which is taken three or four times a day, could possibly increase the risk for potentially fatal heart attack. These findings were based on two studies. The first followed hypertensive patients who had previous heart attacks; the second concentrated on people over the age of 71 who suffered from high BP. All the subjects (except those in the control groups) were taking short-acting nifedipine. Both studies concluded that the risk of heart attack was higher with this drug than with other BP medication. Older people were especially vulnerable, nearly twice as many were
likely to die within five years as those treated with other drugs. Because controversy still surrounds these findings, one should not stop taking this type of nifedipine without consulting your doctor.

In addition to these leading types of BP medication, there are a number of other potent drugs that relax the muscles in the arterial walls, thus lowering BP. Some act directly on the muscles, others work by inhibiting the production or effect of adrenaline, a powerful stimulant released by the body in response to stress. The drugs commonly used are given below:

**Table 8: Other antihypertensives used**

<table>
<thead>
<tr>
<th>Alpha 1 Blockers</th>
<th>Trade Name</th>
<th>Usual Dosage range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prazosin</td>
<td>Minipress®</td>
<td>1-10 mg BID</td>
</tr>
<tr>
<td>Terazosin</td>
<td>Hytrin®</td>
<td>1-20 mg daily</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>Cardura®</td>
<td>1-16 mg daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Central &amp; Peripheral Sympatholytics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reserpine</td>
</tr>
<tr>
<td>Methyldopa</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Direct Vasodilators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
</tr>
<tr>
<td>Minoxidil</td>
</tr>
</tbody>
</table>

Though many of the BP drugs are the result of major scientific breakthroughs, it is all too easy to underestimate their value. There is nothing very magical about the way they work, and they do not, on a day-to-day level, make patients feel demonstrably better. In fact, because hypertension is so often a disease without symptoms, we are usually more aware of the drugs side effects and inconvenience than of their lifesaving properties. But in terms of the number of patients helped, and the number of years added to these patients lives, these drugs rank among the most important of any in use today.

**vi) Second drugs use in hypertensive patients**

From the large controlled studies of the treatment of mild hypertension it is clear that in at least 50% of patients the BP can be controlled with a thiazide alone. The additional drugs used in these studies, for patients not controlled with a thiazide include
Introduction

reserpine in three studies, methyldopa in two studies, hydralazine in two studies, and beta blockers in two studies. We thus can have some confidence in the effectiveness of these drugs used in combination with a thiazide. In patients with moderate to severe hypertension 3 to 4 drugs are often required to adequately control the BP.

vii) Adverse effects associated with various classes of antihypertensives

Adverse effects allied with the various classes of antihypertensives are given below

Table 9: Common adverse effects associated with antihypertensives

<table>
<thead>
<tr>
<th>Common adverse effects</th>
<th>Thiazide Diuretics</th>
<th>Beta blockers</th>
<th>ACE inhibitors</th>
<th>Calcium channel blockers</th>
<th>Angiotensin receptor blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>+</td>
<td>_</td>
</tr>
<tr>
<td>Cough, angioedema</td>
<td>_</td>
<td>_</td>
<td>+</td>
<td>-</td>
<td>_</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>_</td>
<td>+</td>
<td>_</td>
<td>-</td>
<td>_</td>
</tr>
<tr>
<td>Gout</td>
<td>+</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Headache, flushing</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>+</td>
<td>_</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>+</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>_</td>
<td>_</td>
<td>+</td>
<td>_</td>
<td>+</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>+</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Impotence</td>
<td>+</td>
<td>+</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Lethargy</td>
<td>_</td>
<td>+</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Oedema</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>+</td>
<td>_</td>
</tr>
<tr>
<td>Postural</td>
<td>+</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.5.3 TREATMENT VARIES ACCORDING TO THE CHARACTERISTICS OF PATIENTS

i) Hypertension in the elderly

The absolute benefit of treatment is greater in the elderly, patients tolerate BP treatment as well as younger age groups, so studies suggest optimum BP levels should be similar. Beware older people show greater BP variability so more readings may be necessary (including standing BP) and titrate Rx to standing levels. Isolated systolic
hypertension should certainly be treated, although in borderline cases (140-159/<90) without cardiovascular or target organ damage, resource and quality of life issues come to the fore. Use thiazide or nifedipine SR as first line, and ACE II should be used ahead of beta blockers unless specific indications (e.g. angina). Benefits in aged >80 have not been proven but is the subject of current research (Douglas et al, 2003).

ii) Hypertension in the young

Always consider a secondary cause for hypertension (e.g. renal artery stenosis), particularly if difficult to control (consider consultant referral). Framingham risk data is not valid <32 years, and it is extremely unlikely that their CVD 10 year risk will be =20%. Balance long term risk with inconvenience of early treatment.

iii) Idiopathic hypertension in pregnancy

Methyldopa remains the first-line choice, with calcium antagonists (nifedipine) and hydralazine commonly used as second-line. Labetolol is often used for resistant third trimester hypertension. Avoid ACE inhibitors and thiazides.

iv) Hypertension and oral contraceptives:

Generally patients with oral contraceptive pill (OCP) induced hypertension or pre-existing hypertension should use non hormonal contraception, especially if there is co-existent migraine or cardiovascular diseases. If this is unacceptable, switching to the progestogen only contraceptive pill (POP) with careful BP monitoring is recommended.

v) Hormone replacement therapy and Hypertension:

Hormone replacement therapy (HRT) use is not generally associated with increasing BP, and HRT should not be denied hypertensive women as long as BP can be controlled (Williams et al., 2004).

vi) Hypertension and Ethnic groups:

Black African-Caribbeans frequently have severe hypertension which often responds to salt restriction. They are sensitive to diuretics and calcium antagonists, but ACEs and beta blockers are often ineffective as monotherapy, unless used with diuretics, calcium channel blockers or alpha blockers which activate the renin-angiotensin system (Douglas et al, 2003).

vii) Follow up

At least every 6 months, frequency of visits depending on degree of control,
complexity of therapy and compliance. Annual urine analysis for protein, blood for glucose, creatinine and electrolytes (± total and high density lipoprotein (HDL) cholesterol) and evaluation of coronary heart disease (CHD) / CVD risk recommended: with routine visits to measure weight, BP and to enquire about general health, side-effects, treatment problems and to re-inforce non-drug measures. A robust call/recall system is essential.

1.6 DRUG CANDIDATES

1.6.1 PROPRANOLOL HYDROCHLORIDE

Propranolol hydrochloride is a synthetic β-adrenergic receptor blocking agent. Chemical Name: DL-1-(Isopropyl amino)-3-(1-naphthyloxy)-2-propanol hydrochloride. Structure:

\[
\text{OCH}_2\text{CHCH}_2\text{NHCH(CH}_3\text{)CHL}
\]

Molecular Formula: C\text{16}H\text{21}NO\text{2}.HCl

Formula Weight: 295.80  CAS No.: 318-98-9

Elemental composition: C-74.10%  H-8.16%  N-5.4%  O-12.34%

Table 10: Physicochemical data of propranolol hydrochloride

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance and color</td>
<td>White, crystalline solid</td>
</tr>
<tr>
<td>Melting Range</td>
<td>160-164°C</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in water and ethanol, slightly soluble in chloroform and practically insoluble in acetonitrile</td>
</tr>
<tr>
<td>Acidity</td>
<td>9.5 at 24°C</td>
</tr>
<tr>
<td>Partition coefficient</td>
<td>Log P (octanol/pH 7.4) 1.2</td>
</tr>
</tbody>
</table>

Stability:

Propranolol hydrochloride is affected by light. In aqueous solutions, it decomposes with oxidation of the isopropylamine side chain, accompanied by reduction in the pH and discoloration of the solution. Solutions are more stable at pH 3.0 and decompose rapidly under alkaline solutions (The Pharmaceutical Codex, 1994).
i) Mechanism of action

Propranolol hydrochloride is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by propranolol hydrochloride, the chronotropic, inotropic, and vasodilator responses to beta adrenergic stimulation are decreased proportionately (Hoffman and Lefkowitz, 1996).

The mechanism of the antihypertensive effect of propranolol hydrochloride has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output (2) inhibition of renin release by the kidneys and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. Propranolol hydrochloride has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic BP, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta adrenergic blockade, and this appears to be its principal antiarrhythmic mechanism of action. In dosages greater than required for beta blockade, Propranolol hydrochloride also exerts a quinidine like or anesthetic like membrane action, which affects the cardiac action potential.

ii) Pharmacokinetics

a) Absorption

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and half hours. The biologic half-life is approximately 4 h. Propranolol hydrochloride is rapidly
and almost completely absorbed from the intestine. A large part of the absorbed drug is lost to the systemic circulation due to the first pass metabolism in the liver. Peak blood levels occur between 1-3 h after oral administration and will have an average value of 0.1mcg/ml per 80mg single dose. With chronic administration the mean plasma half-life is from 3-6 h, determined by clearance and plasma binding. The pharmacological effect lasts much longer (Clinical pharmacology, 2002).

b) Distribution

Propranolol is absorbed from circulation and is widely distributed throughout the body tissues. Approximately 93% is bound to serum proteins in humans.

c) Metabolism and elimination

Propranolol hydrochloride is rapidly and extensively metabolized and excreted by the liver. Hydroxylation of the aromatic nucleus occurs with degradation of the isoprenaline side chain. Over 20 metabolites have been identified. One of these (4-hydroxypropranolol) found only after oral administration, has beta adrenergic blocking properties.

Some 95-100% of a dose of propranolol hydrochloride is excreted as metabolites and their conjugates in the urine. Small amounts of unchanged propranolol are also excreted in the urine.

Table11: Pharmacokinetic data of propranolol (Hardman and Limbird, 1996)

<table>
<thead>
<tr>
<th>Oral availability (%)</th>
<th>Urinary excretion (%)</th>
<th>Bound in plasma (%)</th>
<th>Clearance (ml min⁻¹ kg⁻¹)</th>
<th>Volume of distribution (liters/kg)</th>
<th>Half life (h)</th>
<th>Effective concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 ± 10</td>
<td>&lt;0.5</td>
<td>87 ± 6</td>
<td>16 ± 5</td>
<td>4.3 ± 0.6</td>
<td>3.9 ± 0.4</td>
<td>20 ng/ml</td>
</tr>
</tbody>
</table>

iii) Adverse effects

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy. In cardiovascular system (CVS) it causes bradycardia, CHF, intensification of atrioventricular (AV) block and hypotension. In CNS, light-headedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, visual disturbances, hallucinations, vivid dreams, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. In GIT,
it causes nausea, vomiting, epigastric distress, abdominal cramping, diarrhea and constipation (Clinical pharmacology, 2002).

iv) Drug interactions

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if propranolol hydrochloride is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity, which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered with a calcium channel blocking drug, especially IV verapamil, both agents may depress myocardial contractility or AV conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, CHF, or recent myocardial infarction.

v) Contraindications

Propranolol should not be used in patients with a known hypersensitivity to the substance. It should not be used in the presence of second or third degree heart block. Propranolol should not be used in patients with cardiogenic shock, uncontrolled heart failure, hypotension, severe peripheral arterial circulatory disturbances, sinus bradycardia or sick sinus syndrome (Clinical pharmacology, 2002).

vi) Doses used for various diseases

a) Hypertension

Dosage must be individualized. The usual initial dosage is 40 mg propranolol hydrochloride twice daily, whether used alone or added to a diuretic. Dosage may be increased gradually until adequate BP control is achieved. The usual maintenance dosage is 120 mg to 240 mg per day. In some instances a dosage of 640 mg a day may be required. The time needed for full antihypertensive response to a given dosage is variable and may range from a few days to several weeks.

b) Angina pectoris

Dosage must be individualized. Total daily doses of 80 mg to 320 mg, when administered orally, twice a day, three times a day, or four times a day, have been shown
to increase exercise tolerance and to reduce ischemic changes in the electrocardiogram (ECG). If treatment is to be discontinued, reduce dosage gradually over a period of several weeks.

c) Arrhythmias

Dose must be 10 mg to 30 mg three or four times daily, before meals and at bedtime.

d) Myocardial infarction

The recommended daily dosage is 180 mg to 240 mg per day in divided doses (Clinical Pharmacology, 2002).

1.6.2 ATENOLOL

Atenolol is an β-adrenolytic, cardio selective drug, having no intrinsic sympathomimetic activity.

Chemical Name: (Rs)–4 –(2-hydroxy-3-isopropylamino-propoxy) phenylacetamide

Structure:

\[
\text{OH} \\
\text{OCH}_2\text{CHCH}_2\text{NHCH(CH}_3)_2 \\
\text{CH}_2\text{CONH}_2
\]

CAS N0. 29122-68-7

Molecular formula: C\(_{14}\)H\(_{22}\)N\(_2\)O\(_3\)

Formula weight: 266.34

Elemental composition: C- 63.13%  H- 8.33%  N- 10.52%  O- 18.02%

<table>
<thead>
<tr>
<th>Appearance, Color, Odor and Taste</th>
<th>White powder, odorless and slightly bitter taste</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting Range</td>
<td>152 – 155°C</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in methanol, soluble in acetic acid, DMSO, sparingly soluble in ethanol and water</td>
</tr>
<tr>
<td>Acidity</td>
<td>9.6 at 24°C</td>
</tr>
<tr>
<td>Partition coefficient</td>
<td>Octanol/ water: 0.23</td>
</tr>
</tbody>
</table>
Stability

Atenolol (powder and tablets) at 50-60% relative humidity and 45-50°C for seven days did not show any change when observed by high performance liquid chromatography (HPLC). The material has not shown any change in color or appearance (Caplar et al., 1984).

i) Mechanism of action

Atenolol is a selective β₁ receptor antagonist. It blocks the synthesis of adenylate cyclase thereby prevents the formation of intracellular messenger, cyclic adenosine mono phosphate which activates various protein kinases which control cell function in many ways by causing phosphorylation of various enzymes, carriers and other proteins (Hoffman and Lefkowitz, 1996).

ii) Pharmacokinetics

a) Absorption

In man, absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the GIT, the remaining being excreted unchanged in the faeces. Peak blood levels are reached between 2 and 4 h after ingestion. Following IV administration, peak plasma levels are reached within 5 min. Declines from peak levels are rapid (5 to 10 fold) during the first 7 h, thereafter, plasma levels decay with a half-life similar to that of orally administered drug.

b) Distribution

Small amount (16%) of atenolol is bound to proteins in the plasma.

c) Metabolism

Atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion.

d) Elimination

Over 85% of an IV dose is excreted in urine within 24 h compared with approximately 50% for an oral dose. The elimination half life of oral atenolol is approximately 6 to 7 h, and there is no alteration of the kinetic profile of the drug by chronic administration. When renal function is impaired, elimination of atenolol is closely related to the glomerular filtration rate.
Table 13: Pharmacokinetic data of atenolol (Hardman and Limbird, 1996)

<table>
<thead>
<tr>
<th>Oral availability (%)</th>
<th>Urinary excretion (%)</th>
<th>Bound in plasma (%)</th>
<th>Clearance (ml min(^{-1}) kg(^{-1}))</th>
<th>Volume of distribution (liters/kg)</th>
<th>Half life (h)</th>
<th>Effective concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>56 ± 30</td>
<td>94 ± 8</td>
<td>&lt;5</td>
<td>2.0 ± 0.2</td>
<td>0.95 ± 0.15</td>
<td>6.1 ± 2.0</td>
<td>0.1-1.0 µg/ml</td>
</tr>
</tbody>
</table>

iii) Adverse effects

Most adverse effects have been mild and transient. In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta blocker, in atenolol treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol (Clinical pharmacology, 2005).

iv) Drug interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta blocking agents. Patients treated with atenolol plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Calcium channel blockers may also have an additive effect when given with atenolol. Beta blockers may exacerbate the rebound hypertension, which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta blocker therapy, the introduction of beta blockers should be delayed for several days after clonidine administration has stopped.

v) Contraindications

Atenolol is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.
vi) Doses used for various diseases

a) Hypertension

The initial dose of atenolol is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

Atenolol may be used alone or concomitantly with other antihypertensive agents including thiazide type diuretics, hydralazine, prazosin, and alpha-methyldopa.

b) Angina pectoris

The initial dose of atenolol is 50 mg given as one tablet a day. If an optimal response is not achieved within one week, the dosage should be increased to 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

c) Acute myocardial infarction

Treatment begins with the IV administration of 5 mg atenolol over 5 min followed by another 5 mg intravenous injection 10 min later atenolol IV injection should be administered under carefully controlled conditions including monitoring of BP, heart rate, and ECG.

d) Elderly patients or patients with renal impairment

Atenolol is excreted by the kidneys; consequently dosage should be adjusted in cases of severe impairment of renal function. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (Clinical pharmacology, 2005).
1.6.3 METOPROLOL TARTRATE

Metoprolol tartrate is a synthetic, selective $\beta_1$-adrenoceptor blocking agent.

Chemical Name: 1-(isopropylamino)-3-[p-(beta-methoxyethyl) phenoxy]2-propanol tartrate salt

Structure:

\[
\text{OCH}_2\text{CHCH}_2\text{NHCH}(\text{CH}_3)_2\quad \text{COOH}
\]

\[
\text{CH}_2\text{OCH}_3\quad \text{CH}_2\text{OH}\quad \text{CHOH}\quad \text{COOH}
\]

Molecular Formula: $(\text{C}_{15}\text{H}_{25}\text{N}_3)_2 \cdot \text{C}_4\text{H}_6\text{O}_6$

Formula Weight: 684.82

CAS No: 56392-17-7

Elemental composition: C- 59.63%  H- 8.24%  N- 4.09%  O- 28.04%

Table 14: Physicochemical data of metoprolol tartrate

<table>
<thead>
<tr>
<th>Appearance, Color and Odor</th>
<th>White, virtually odorless crystalline powder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting Range</td>
<td>123-125°C</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in water, methanol and insoluble in acetonitrile.</td>
</tr>
<tr>
<td>Acidity</td>
<td>9.68 at 25°C</td>
</tr>
<tr>
<td>Partition coefficient</td>
<td>Octanol/pH 7.4: 0.587</td>
</tr>
</tbody>
</table>

Stability

a) Solid state stability

Metoprolol tartrate stored at room temperature and at 35°C for five years is physically and chemically stable. After storage at 50°C for up to thirty months, no degradation has been observed- the only change has been that the material became slightly off-white: at lower temperatures and at shorter time intervals at 50°C, it has been completely unchanged in color. Under high humidity metoprolol tartrate is hygroscopic and rapidly absorbs water at relative humidities greater than 70%; however, upon drying
and reanalysis, the material is found to have retained its chemical and physical integrity.

b) Solution stability

No chemical change has been observed for solutions of metoprolol tartrate buffered at pH values of 4, 7, and 9, which have been stored at 60°C for 10 days. Metoprolol tartrate solutions prepared in 0.1N HCl, pH 7 phosphate buffer and 0.1N sodium hydroxide when refluxed for 20 h with no evidence of chemical change (Luch, 1983).

i) Mechanism of action

Metoprolol tartrate is a β adrenergic receptor blocking agent. Metoprolol tartrate acts by blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in BP, it reduces the oxygen requirements of the heart at any given level of effort, thus making useful in the long-term management of angina pectoris. However, in patients with heart failure, β-adrenergic receptor blockade may increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure (Hoffman and Lefkowitz, 1996).

ii) Pharmacokinetics

a) Absorption

In humans, absorption of metoprolol tartrate is rapid and complete. Plasma levels following oral administration, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism. Peak plasma concentrations are attained after approximately 1.5-2 h with conventional metoprolol formulations, and after approximately 4-5 h with slow-release formulations. Upon repeated oral administration, the percentage of the dose systemically available is higher than after a single dose and also increases dose dependently. Ingestion with food may raise the systemic availability of an oral dose by approximately 20-40% (Clinical pharmacology, 2003).

b) Distribution

Only a small fraction of the drug (12%) is bound to human serum albumin.

c) Metabolism

Metoprolol tartrate is extensively metabolized by enzymes of the cytochrome P450 system in the liver. The oxidative metabolism of this is under genetic control with a
major contribution of the polymorphic cytochrome P450 isoform 2D6 (CY2D6). However, the cytochrome P450 2D6 dependent metabolism seems to have little or no effect on safety or tolerability of the drug. None of the metabolites contribute significantly to its β-blocking effect.

\(d)\) Elimination

Elimination is mainly by biotransformation in the liver, and the plasma half-life averages 3.5 h. The total clearance rate of an IV dose is approximately 1L/min and the protein binding rate is approximately 10%. Less than 5% of an oral dose of metoprolol tartrate is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance.

**Table 15: Pharmacokinetic data of metoprolol** (Hardman and Limbird, 1996)

<table>
<thead>
<tr>
<th>Oral availability (%)</th>
<th>Urinary excretion (%)</th>
<th>Bound in plasma (%)</th>
<th>Clearance (ml min(^{-1}) kg(^{-1}))</th>
<th>Volume of distribution (liters/kg)</th>
<th>Half life (h)</th>
<th>Effective concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>38 ± 14</td>
<td>10 ± 3</td>
<td>11 ± 1</td>
<td>15 ± 3</td>
<td>4.2 ± 0.7</td>
<td>3.2 ± 0.2</td>
<td>16 ± 7 mg/ml</td>
</tr>
</tbody>
</table>

\(iii)\) Adverse effects

Most adverse effects have been mild and transient. In CNS, it causes tiredness, dizziness, headache, nightmares, and insomnia. In CVS, shortness of breath, bradycardia, cold extremities, arterial insufficiency, palpitations, CHF, peripheral edema and hypotension. In respiratory system, wheezing (bronchospasm) and dyspnea.

\(iv)\) Drug interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with metoprolol tartrate plus a catecholamine depletor should, therefore, be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension (Clinical pharmacology, 2003).

While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge by accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.
v) Contraindications

Metoprolol tartrate is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

vi) Doses used for various diseases

a) Hypertension

The dosage of metoprolol tartrate should be individualized. Metoprolol tartrate should be taken with or immediately following meals. The usual initial dosage is 100 mg daily in single or divided doses, whether used alone or added to diuretic. The dosage may be increased at weekly (or longer) intervals until optimum BP reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. The effective dosage range is 100-450 mg per day. Dosages above 450 mg per day have not been studied. While once-daily dosing is effective and can maintain a reduction in BP throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24 h period, and larger or more frequent daily doses may be required. This can be evaluated by measuring BP near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day.

b) Angina pectoris

The usual initial dose is 100 mg daily, given in two divided doses. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is pronounced slowing of the heart rate. The effective dosage range is 100-400 mg per day. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1 to 2 weeks.

c) Myocardial infarction

During the early phase of definite or suspected acute myocardial infarction, treatment with metoprolol tartrate can be initiated and should begin with the IV administration of three bolus injections of 5 mg of metoprolol tartrate each, the injections should be given at approximately 2 min intervals. During the IV administration of metoprolol tartrate, BP, heart rate, and ECG should be carefully monitored. Patients with contraindications to treatment during the early phase of suspected or definite myocardial infarction should be started with metoprolol tartrate tablets, 100 mg twice daily and should be continued for at least 3 months (Clinical pharmacology, 2003).