CHAPTER - 4

LITERATURE REVIEW

4.1. SKIN ANATOMY AND PHYSIOLOGY

4.1.1 Skin layers

   Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration (Guy, 1996). Skin is the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. The human skin consists of two major layers; the epidermis and the dermis. The epidermis is a keratinized squamous epithelium; its surface consists of dead cells packed with the tough protein keratin. The keratinocytes comprise the major cellular component and are responsible for a barrier function. The epidermis consists of five layers which correspond to the consecutive steps of keratinocyte differentiation:

   (1) Stratum basale consists of a single layer of cuboidal to low columnar cells resting on the basement membrane of the epithelium. Proliferation of the stem cells in the stratum basale creates new keratinocytes which then push existing cells towards the surface.

   (2) Stratum spinosum consists of several layers of keratinocytes, that have the numerous spiny projections on the cell surface.

   (3) Stratum granulosum consists of two to five layers of flat keratinocytes that produce lipid filled membrane-coating vesicles.

   (4) Stratum lucidum consists of a thin translucent zone superficial to the stratum granulosum. The keratinocytes are density packed with eleidin, an intermediate stage in the production of keratin.

   (5) Stratum corneum is composed of the flattened remnants of the skin cell (corneocytes), surrounded by a multilamellar system of long chain lipids.

   The dermis, at 3-5 mm thickness, is composed mainly of collagen but also contains elastic and reticular fibers, the usual cells of fibrous connective tissue and
blood vessels, sweat glands, sebaceous glands, hair follicles, nail roots and sensory nerve endings. The structure of the skin is shown in Figure 4.1

![Cross-section of the uppermost layers of human skin](image)

**Figure 4.1:** Cross-section of the uppermost layers of human skin (Subbu and Robert, 1998)

### 4.1.2 Routes of the skin penetration

There are potentially two possible pathways of permeation for drugs; an appendageal pathway and a transepidermal pathway (Figure 4.2).

1. The appendages of the skin are composed of sweat glands, hair follicles and the associated sebaceous glands which the hair follicles are the major appendages for permeation. For electrolytes and large molecules with low diffusion coefficients, such as polar steroids and antibiotics and for some colloidal particles, the appendages may provide the main entry route. The appendageal pathway is thought to be of primary importance in drug permeation when iontophoresis is used.

2. The transepidermal pathway: The stratum corneum is the predominant barrier limiting the diffusion of the drugs into deeper layers of the skin. This layer is thought
of as a “brick wall”, with the fully differentiated corneocytes comprising the brick, embedded in the motar created by the intercellular lipids. The corneocytes are filled with a matrix of crosslinked keratin filaments, responsible for mechanical stability of the stratum corneum. The intercellular lipids of the stratum corneum comprise a mixture of ceramide (55%), cholesterol (25%), cholesterol sulphate (5%) and fatty acid (15%). These nonpolar and rigid components of the stratum corneum’s “cement” play a critical role in barrier function. The transepidermal pathway consists of two penetration route, there are intracellular route and intercellular route.

**Figure 4.2:** Routes of drug permeation in the stratum corneum (Suhonen et al., 1998)

In intracellular route, the transport process is the permeant partitioning into the keratinocyte, followed by diffusion through the hydrated keratin. In order to leave the cell, the permeant must partition into the lipid bilayers before diffusing across the lipid bilayer to the next keratinocyte.

The intercellular route is principal transport pathway for the small unchanged molecules. This route is most tortuous which the permeant moving through the continuous lipid bilayer domain between the keratinocytes, so the path length taken by the permeant is greater than that the stratum corneum thickness. Various estimates have been proposed for the intercellular permeation distance ranging from 150 to 500 μm.
The fraction of a drug that penetrates the skin via any particular route depends on: the physicochemical of the drug, particularly its size, solubility and partition coefficient; the site and condition of the skin; the formulation and how vehicle components temporarily change the properties of the stratum corneum. The ideal properties that a molecule would require so as to penetrate the stratum corneum well are:

- Allow molecular mass, preferably less than 600 Da, when the diffusion coefficient will tend to be high.
- An adequate solubility in oil and water, so that the concentration gradient in the skin and be high.
- A balanced partition coefficient.
- A low melting point, this correlates with good ideal solubility.

4.1.3 Factors affecting transdermal bioavailability

The factors which affect the transdermal bioavailability of a drug can be classified as (Chung, 1999)

- Physiological factors
- Formulation factors

a. Physiological factors

Stratum corneum: It is important to note that the principal function of the stratum corneum is to act as a barrier. So to improve transdermal bioavailability, strategies to change the composition or the organization of intercellular lipids have been developed.

Age: The rate of transepidermal water loss across the skin changes because of the change in texture of skin with age. As the skin ages it becomes progressively more fragile, therefore more sensitive to the removal of well adhered transdermal patch. Whereas the skin of premature neonates (born at less than 30 weeks of gestational age) have poorly developed barriers and are at risk for many problems including percutaneous intoxication.

Skin metabolism: Also known as “cutaneous first pass effect”. Presystemic metabolism in the skin can obviously modify transdermal bioavailability. The
cutaneous first pass effect for nitro-glycerine, for example has been estimated to be 15-20%. The viable epidermis is a biochemically active tissue with low metabolic capability. Indeed, a multitude of enzymes has been identified in the skin, including a cytochrome P450 system.

**Desquamation:** This corresponds to shedding of one layer of the stratum corneum per day. This is a critical factor for patches which delivers the drug for more than 24h.

**Skin irritation and sensitization:** If a drug is a frank irritant, there is little to save its candidacy for transdermal delivery. Sensitization is equally great problem

**Half life of drug:** Transdermal patches are for sustained delivery so the drugs with short half life are more beneficial to be formulated into transdermal patches.

**b. Formulation factors:** Physical chemistry of transport: In order to maximize permeation, one must use a formulation saturated with drug. This will enable the flux to be as large as possible.

**Partition coefficient:** Usually lipophillic drugs are favoured, but one has to strike a balance between partition coefficient and drug loading so that leaving tendency of drug from the formulation favors its efficient movement into the skin but at the same time the saturation solubility of drug in the vehicle is high enough so that sustained delivery can be achieved for intended time of application.

**Lipophillicity:** It is key factor for drug acceptance by the stratum corneum and most of the transdermally delivered drugs have log partition coefficient in the range of 0.8-3.3.

### 4.2. SYSTEM SPECIFIC REVIEW – TDDS

With the advent of new era of pharmaceutical dosage forms, TDDS established itself as an integral part of novel drug delivery system. Delivering medicine transdermally is seen as a desirable alternative to oral administration. In addition to increasing convenience, transdermal delivery can change the metabolism and bioavailability of compounds and their metabolites and thus alter the therapeutic index of a particular drug. Because of the reduced frequency of administration, compliance
should be enhanced with transdermal delivery. Delivery of drug via transdermal route also avoids the hostile environment of gastrointestinal tract, where drugs can be inactivated and absorption can vary depending on pH, food ingestion/interaction, and other factors. In addition, oral medications may cause nausea because of local effects, and some cannot be taken if the patient is already nauseated. Transdermal route also avoids hepatic first-pass metabolism and associated side effects. This can be exemplified with oxybutynin, a drug useful in treatment of overactive bladder. Oxybutynin undergoes presystemic metabolism within small intestine and then primarily through hepatic first pass metabolism, before it enters the circulatory system. So a percentage of the parent drug is converted to metabolite before reaching the target site i.e., bladder or other organs responsible for side effects – primarily, the salivary gland, bowel, eye and brain. Transdermal administration essentially bypasses this initial presystemic metabolism and causes fewer side effects than oral form of the drug (David et al., 2003).

We might better understand the potential benefits and role of transdermal systems by considering the experience already gained with those currently available, particularly with respect to patient and physician satisfaction. It is important for the psychiatrists to understand the advantages and disadvantages of transdermal therapy in general and for psychotropic drugs specifically. Furthermore, some insights into how transdermal therapy can be enhanced in the future will provide an even greater understanding of its potential.

Transdermal hormone replacement therapy (HRT) has been available for years and is accepted alternative to oral therapy. There have been numerous studies comparing transdermal versus oral HRT with respect to a variety of efficacy variables (Corson, 1993; Powers et al., 1985).

Ettinger et al., (1998) found that 25% of women who started on oral therapy of estrogens switched to transdermal estradiol versus 0.9% who switched from transdermal to oral therapy.

Lake and Pinnock (2000) compared 2 different types of estradiol, matrix versus reservoir, in 35 hysterectomized women who received 4 weeks of each therapy. 87% of patients selected the matrix patch because it was easy to apply, open and had better
adhesion and cosmetic appearance. Of 27 subjects who stated a preference, 74% preferred transdermal to oral therapy.

Transdermal delivery of contraception is also becoming popular. Since its introduction in 2002, the Ortho Evra™ once weekly patch has become the fastest growing contraceptive on the market. Various trials showed superior compliance with patch as compared to oral contraceptives (Audet et al., 2001; Hedon et al., 2000). Another data showed that compliance with the patch was consistent across age groups but differed significantly by age for oral therapy, with younger patients having a lower percentage of cycles with perfect compliance (Archer et al., 2002).

Transdermal delivery has also become popular for the treatment of chronic cancer related and non cancer pain. Two studies on chronic pain in patients with advanced cancer showed a patient preference for transdermal fentanyl versus sustained release oral morphine. Although both treatments resulted in similar relief of pain, but transdermal delivery of fentanyl was associated with a lower frequency and reduced side effects (Ahmedzai and Brooks, 1997; Payne et al., 1998). Allan et al., (2001) studied transdermal fentanyl versus oral sustained release morphine for the treatment of non cancer pain. Preference was assessed in 85% of 256 patients, of which 65% preferred transdermal therapy and 28% preferred oral therapy and 7% expressed no preference. Quality of life scores were higher in the group receiving transdermal therapy. Available data suggests the acceptance of transdermal therapy for various diseased conditions because of its convenience and decreased incidence and impact of side effects. Table 4.1 enlists the commercially available transdermal formulations (Aggarwal and Dhawan, 2009a).

### 4.2.1 Basic components of TDDS

- Polymer matrix / Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates
- Release liner
- Other excipients like plasticizers and solvent
<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Type of transdermal patch</th>
<th>Manufacturer</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>Duragesic</td>
<td>Reservoir</td>
<td>Alza / Janssen Pharmaceutica</td>
<td>Moderate/Severe pain</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Deponit and Minitran</td>
<td>Drug in adhesive</td>
<td>Schwarz Pharma and 3M Pharmaceuticals</td>
<td>Angina Pectoris</td>
</tr>
<tr>
<td>Nitrodisc</td>
<td>Micro reservoir</td>
<td></td>
<td>Searle, USA</td>
<td></td>
</tr>
<tr>
<td>Nitrodur</td>
<td>Matrix</td>
<td></td>
<td>KeyPharmaceuticals</td>
<td></td>
</tr>
<tr>
<td>Transderm Nitro</td>
<td>Reservoir</td>
<td></td>
<td>Alza/Novartis</td>
<td></td>
</tr>
<tr>
<td>Nicotine</td>
<td>Prostep</td>
<td>Reservoir</td>
<td>ElanCorp/Lederie Labs</td>
<td>Smoking Cessation</td>
</tr>
<tr>
<td>Nicotrol</td>
<td>Drug in adhesive</td>
<td></td>
<td>Cygnus Inc./McNeil Consumer Products Ltd</td>
<td></td>
</tr>
<tr>
<td>Habitrol</td>
<td>Drug in adhesive</td>
<td></td>
<td>Novartis</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>Androderm</td>
<td>Reservoir</td>
<td>Thera Tech/ GlaxoSmithKline/Alza</td>
<td>Hypogonadism in males</td>
</tr>
<tr>
<td>Testoderm</td>
<td>Drug in adhesive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTS</td>
<td>Drug in adhesive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>Catapres-TTS</td>
<td>Membrane matrix hybrid type</td>
<td>Alza/Boehinger Ingelheim</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Lidoderm</td>
<td>Drug in adhesive</td>
<td>Cerner Multum, Inc.</td>
<td>Anesthetic</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Transderm Scop</td>
<td>Membrane matrix hybrid type</td>
<td>Alza/Novartis</td>
<td>Motion sickness</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Climara</td>
<td>Drug in adhesive</td>
<td>3M Pharmaceuticals/Berlex Labs</td>
<td>Postmenstrual Syndrome</td>
</tr>
<tr>
<td>Ethinyl Estradiol</td>
<td>Vivelle</td>
<td></td>
<td>Noven Pharma/Novartis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Estraderm</td>
<td>Reservoir</td>
<td>Alza/Novartis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Esclim</td>
<td>Drug in adhesive</td>
<td>Women First Healthcare, Inc. Johnson &amp; Johnson</td>
<td></td>
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<tr>
<td></td>
<td>Ortho Evra</td>
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</table>

4.2.1.1. Polymer matrix / Drug reservoir: Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in
TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers and PSAs. Additionally they should provide consistent and effective delivery of a drug throughout the product’s intended shelf life and should be of safe status (Keith, 1983).

Companies involved in the field of transdermal delivery concentrate on a few selective polymeric systems. For example, Alza Corporation mainly concentrates on ethylene vinyl acetate (EVA) copolymers or microporous polypropylene and Searle Pharmacia concentrates on silicon rubber (Baker and Heller, 1989). Similarly Colorcon, UK uses hydroxypropyl methylcellulose (HPMC) for matrix preparation for propranolol transdermal delivery and Sigma uses ethylcellulose for isosorbide dinitrate matrix (Gabiga et al., 2000; Guyot and Fawaz, 2000; Minghetti et al., 1999). The polymers utilized for TDDS can be classified as (Guy 1987; 1996):

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

The polymers like cross linked polyethylene glycol (Bromberg, 1996), eudragits (Verma et al., 2000), ethyl cellulose, polyvinylpyrrolidone (Ubaidulla et al., 2007) and HPMC (Gannu et al., 2007) are used as matrix formers for TDDS. Other polymers like EVA (Gale and Spitze, 1981), silicon rubber and polyurethane (Boretos et al., 1971) are used as rate controlling membrane.

**4.2.1.2 Drug**: The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non-compliance due to frequent dosing. The foremost requirement of TDDS is that the drug possesses the right mix of physicochemical and biological properties for transdermal drug delivery (Chung et al., 1999; Izumoto et al., 1992). It is generally accepted that the best drug candidates for passive adhesive
transdermal patches must be non ionic, of low molecular weight (less than 500 Daltons), have adequate solubility in oil and water (log P in the range of 1-3), a low melting point (less than 200°C) and are potent (Gordon and Peterson, 2003).

4.2.1.3 Permeation Enhancers: These are the chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate (Williams and Barry, 2004). Penetration enhancers interact with structural components of stratum corneum i.e., proteins or lipids. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability (Karande et al., 2005). Over the last 20 years, a tremendous amount of work has been directed towards the search for specific chemicals, combination of chemicals, which can act as penetration enhancers. Some of the permeation enhancers have been enlisted in Table 4.2.

Table 4.2: Permeation enhancers used for TDDS

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvents</td>
<td>Methanol</td>
<td>Thornfeldt 1998</td>
</tr>
<tr>
<td></td>
<td>Ethanol</td>
<td>Ning et al., 2007</td>
</tr>
<tr>
<td></td>
<td>Dimethyl sulfoxide</td>
<td>Budhathoki and Thapa, 2005</td>
</tr>
<tr>
<td></td>
<td>Propylene glycol</td>
<td>Zurdo et al., 2007</td>
</tr>
<tr>
<td></td>
<td>2- Pyrrrolidone</td>
<td>Babu et al., 2005</td>
</tr>
<tr>
<td></td>
<td>Isopropyl myristate</td>
<td>Oquiso et al., 1995</td>
</tr>
<tr>
<td></td>
<td>Laurocapram (Azone)</td>
<td>Parikh and Ghosh, 2005</td>
</tr>
<tr>
<td>Anionic surfactants</td>
<td>Sodium lauryl sulphate</td>
<td>Nokodchi et al., 2003</td>
</tr>
<tr>
<td>Nonionic surfactants</td>
<td>Sorbitan monolaurate</td>
<td>Mukherjee et al., 2005</td>
</tr>
<tr>
<td></td>
<td>Pluronic</td>
<td>El-Kattan et al., 2000</td>
</tr>
<tr>
<td>Essential oils</td>
<td>Cardamom oil</td>
<td>Huang et al., 1999</td>
</tr>
<tr>
<td></td>
<td>Caraway oil, Lemon oil</td>
<td>Kaza and Pitchaimani, 2006</td>
</tr>
<tr>
<td></td>
<td>Menthol</td>
<td>Giannakou et al., 1998</td>
</tr>
<tr>
<td></td>
<td>d-limonene</td>
<td>Jayaaraam et al., 2004</td>
</tr>
<tr>
<td></td>
<td>Linoleic acid</td>
<td>Shin et al., 2000</td>
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</tbody>
</table>
4.2.1.4. Pressure sensitive adhesives: A PSA is a material that helps in maintaining an intimate contact between transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy, and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue (Pocius, 1991; Walters, 1997). Polyacrylates, polyisobutylene and silicon based adhesives are widely used in TDDSs (Franz, 1991). The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. For matrix systems with a peripheral adhesive, an incidental contact between the adhesive and the drug and penetration enhancer should not cause instability of the drug, penetration enhancer or the adhesive. In case of reservoir systems that include a face adhesive, the diffusing drug must not affect the adhesive. In case of drug-in-adhesive matrix systems, the selection will be based on the rate at which the drug and the penetration enhancer will diffuse through the adhesive. Ideally, PSA should be physicochemically and biologically compatible and should not alter drug release (Tan and Pfister, 1999).

4.2.1.5. Backing laminate: While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipient compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. However, an overemphasis on the chemical resistance may lead to stiffness and high occlusivity to moisture vapor and air, causing patches to lift and possibly irritate the skin during long wear. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapor transmission rate (Godbey, 1996; Pfister and Hsieh, 1990). Examples of some backing materials are vinyl, polyethylene and polyester films.

4.2.1.6. Release liner: During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. Typically,
release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or Teflon. Other materials used for TDDS release liner include polyester foil and metallized laminates (Khatun et al., 2004; Walters, 1997).

4.2.1.7. Other excipients: Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir (Gannu et al., 2007; Khatun et al., 2004). In addition plasticizers such as dibutylphthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch (Gondaliya and Pundarikakshudu, 2003; Rao and Diwan, 1997).

4.2.2. Design and fabrication of transdermal patches

The development of TDDS is multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of drug molecule to the demonstration of sufficient drug flux in an ex vivo and in vivo model followed by fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical and stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most important the economy (Kandavilli et al., 2002).

Several system designs have been used in development and fabrication of TDDSs. The systems that have been introduced in market can be classified into following types (Davis, 1992; Godbey et al., 1996):

- Matrix type
- Reservoir type
- Membrane matrix hybrid
- Micro reservoir type
- Drug in adhesive type

4.2.2.1 Matrix type transdermal patch(es): Drug reservoir is prepared by dissolving the drug and polymer in a common solvent. The insoluble drug should be homogenously dispersed in hydrophilic or lipophillic polymer. The required quantity of plasticizer like dibutylphthalate, triethylcitrate, polyethylene glycol or propylene glycol and permeation enhancer is then added and mixed properly. The medicated polymer formed is then molded into rings with defined surface area and controlled
thickness over the mercury on horizontal surface followed by solvent evaporation at an elevated temperature. The film formed is then separated from the rings, which is then mounted onto an occlusive base plate in a compartment fabricated from a drug impermeable backing. Adhesive polymer is then spread along the circumference of the film (Costa et al., 1997; Mutalik et al., 2005). Some examples of matrix patches prepared by solvent evaporation method mentioned in literature are given in Table 4.3. Commonly used polymers for matrix are cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose.

The dispersion of drug particles in the polymer matrix can be accomplished by either homogenously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of polymer chains or homogenously blending drug solids with a rubbery polymer at an elevated temperature (Misra, 1997). The matrix system is exemplified by the development of Nitro-Dur®. Advantages of matrix patches include absence of dose dumping, direct exposure of polymeric matrix to the skin and no interference of adhesive. Design of matrix type patch is shown in Figure 4.3

**Figure 4.3:** Design of matrix type transdermal patch

**4.2.2.2 Reservoir type transdermal patch(s):** The drug reservoir is made of a homogenous dispersion of drug particles suspended in an unleachable viscous liquid medium (e.g. silicon fluids) to form a paste like suspension or gel or a clear solution of drug in a releasable solvent (e.g. ethanol). The drug reservoir formed is sandwiched between a rate controlling membrane and backing laminate (Chien et al., 1983). The rate controlling membrane can be nonporous so that the drug is released by diffusing directly through the material, or the material may contain fluid filled micropores in which case the drug may additionally diffuse through the fluid, thus
Table 4.3: Examples of matrix patches prepared by solvent evaporation method reported in literature

<table>
<thead>
<tr>
<th>Drug</th>
<th>Polymer</th>
<th>Solvent</th>
<th>Permeation enhancer</th>
<th>Plasticizer</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline and salbutamol</td>
<td>PEG 400</td>
<td>Water</td>
<td>Nil</td>
<td>Nil</td>
<td>Murthy and Hiremath, 2001</td>
</tr>
<tr>
<td>Salbutamol sulphate</td>
<td>Eudragit RL100</td>
<td>Isopropanol: water 6:4</td>
<td>Dimethyl sulfoxide, Isopropyl myristate, Tween80, Sodium lauryl sulfate with propylene glycol</td>
<td>Nil</td>
<td>Budhathoki et al., 2005</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Ethylcellulose: Polyvinyl pyrrolidone and Eudragit RL100: Eudragit RS100</td>
<td>Chloroform</td>
<td>Nil</td>
<td>Di-n-butyl phthalate</td>
<td>Ubaidulla et al., 2007</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>Ethylcellulose: polyvinyl pyrrolidone</td>
<td>Chloroform</td>
<td>Nil</td>
<td>Nil</td>
<td>Mutalik and Udupa, 2004</td>
</tr>
<tr>
<td>Naproxan</td>
<td>Eudragit RS100</td>
<td>Dichloromethane</td>
<td>PEG</td>
<td>Span 80</td>
<td>Khatun et al., 2004</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>Eudragit RL100: HPMC and Eudragit RS100: HPMC</td>
<td>Dichloromethane: Methanol</td>
<td>Carvone</td>
<td>Propylene glycol</td>
<td>Gannu et al., 2007</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Eudragit NE 30D</td>
<td>Polyvinyl alcohol</td>
<td>Nil</td>
<td>Nil</td>
<td>Samanta et al., 2003</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Eudragit RL PM</td>
<td>2-Propanol</td>
<td>Benzalkonium chloride, sodium lauryl sulfate</td>
<td>Nil</td>
<td>Costa et al., 1997</td>
</tr>
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</table>
filling the pores. In the case of nonporous membrane, the rate of passage of drug molecules depends on the solubility of the drug in the membrane and the thickness of membrane. Hence, the choice of membrane material is dependent on the type of drug being used. By varying the composition and thickness of the membrane, the dosage rate per unit area of the device can be controlled. Mostly EVA, ethyl cellulose, silicon rubber and polyurethanes are used to prepare rate controlling membranes (Lewis et al., 2006; Liang et al., 1990; Krishna and Pandit, 1994). EVA is used most frequently to prepare rate controlling membrane in transdermal delivery systems because it allows the membrane permeability to be altered by adjusting vinyl acetate content of polymer. Polyurethane membranes are suitable especially for hydrophobic polar compounds having low permeability through hydrophobic polymers such as silicon rubber or EVA membrane (Baker, 1979).

Liang et al., (1990) studied controlled release of scopolamine through EVA membrane in transdermal patch formulations and release rates were compared with uncontrolled reservoirs. It was found that an EVA membrane patch released scopolamine at a constant rate for more than 72 hours. Krishna and Pandit (1994) prepared three transdermal formulations containing propranolol hydrochloride in a hydrophilic polymer matrix, one without rate controlling membrane and other two with EVA rate controlling membranes of different thickness. It was found that increased thickness of EVA led to greater retention of the drug in device and zero order profile was observed with EVA.

Rate controlling membrane may be prepared by solvent evaporation method or compression method. In case of solvent evaporation method, polymer is dissolved in solvent with or without plasticizer. Then the solution is poured on the horizontal surface and left for evaporation of solvent in order to obtain a thin film. Examples of preparation of rate controlling membrane by solvent evaporation method are shown in Table 4.4. In case of compression method, polymer is compressed with required force at high temperature for specific period of time (Arabi et al., 2002). Drugs that require relatively high doses or greater permeation enhancement, such as testosterone, use liquid reservoir systems. But the application of enhancers and adhesive technologies has allowed many drugs that were initially administered in liquid reservoirs to be used as
matrix type systems e.g. estradiol, nicotine, nitroglycerine (David, 2003). The main advantage of reservoir type patches is that this patch design can provide a true zero order release pattern to achieve a constant serum drug level. Examples of marketed preparations are Duragesic®, Estradem® and Androderm®. Figure 4.4 illustrates the design of reservoir type of patch.

Figure 4.4: Design of reservoir type transdermal patch

Table 4.4: Examples of rate controlling membrane prepared by solvent evaporation method for reservoir type transdermal patches

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rate controlling membrane</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopolamine</td>
<td>EVA, Toluene</td>
<td>Arabi et al., 2002</td>
</tr>
<tr>
<td>Nicotine</td>
<td>EC, Chloroform and dichloromethane, Dibutyl phthalate</td>
<td>Lewis et al., 2006</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>EC, Methylene chloride</td>
<td>Arabi et al., 2002</td>
</tr>
</tbody>
</table>

4.2.2.3 Membrane matrix hybrid type patch(s): This is the modification of reservoir type transdermal patch. The liquid formulation of the drug reservoir is replaced with a solid polymer matrix (e.g. polyisobutylene) which is sandwiched between rate controlling membrane and backing laminate (Foco et al., 2004). Examples of marketed preparations are Catapress® and TransdermScop®.

4.2.2.4 Micro reservoir type transdermal patch(s): The drug reservoir is formed by suspending the drug solids in an aqueous solution of water miscible drug solubilizer e.g. polyethylene glycol. The drug suspension is homogenously
dispersed by a high shear mechanical force in lipophillic polymer, forming thousands of unleachable microscopic drug reservoirs (micro reservoirs). The dispersion is quickly stabilized by immediately cross linking the polymer chains in-situ which produces a medicated polymer disc of a specific area and fixed thickness. Occlusive base plate mounted between the medicated disc and adhesive form backing prevents the loss of drug through the backing membrane (Chien et al., 1983; Walter, 2004). This system is exemplified by development of Nitrodisc®. Micro reservoir type transdermal system is shown in Figure 4.5.

![Diagram of micro reservoir type transdermal patch]

**Figure 4.5:** Design of micro reservoir type transdermal patch

**4.2.2.5 Drug in adhesive type transdermal patch(s):** The drug and other selected excipients, if any, are directly incorporated into the organic solvent based pressure sensitive adhesive solution, mixed, cast as a thin film and dried to evaporate the solvents, leaving a dried adhesive matrix film containing the drug and excipients. This drug in adhesive matrix is sandwiched between release liner and backing layer. Drug-in-adhesive patch may be single layer or multi layer. The multi layer system is different from single layer in that it adds another layer of drug-in-adhesive, usually separated by a membrane.

Some examples of suitable pressure sensitive adhesives are polysiloxanes, polyacrylates and polyisobutylene. These pressure sensitive adhesives are hydrophobic in nature and are prepared as solutions of polymer dissolved in organic solvents. Hence, this type of system is preferred for hydrophobic drugs as it is to be incorporated into organic solvent based hydrophobic adhesive (Venkateshwaran et al., 1999). Rachel et al., (2004) prepared drug in adhesive patches of green tea extract and it was observed that major catechins and caffeine extracted from green tea were successfully delivered transdermally from drug-in-adhesive patches. Kannikkanan et
al., (2004) prepared and evaluated monolithic drug in adhesive type transdermal patches of melatonin and used eudragit E100 as adhesive polymer. Lake and Pinnock (2000) proved that once a week drug in adhesive patch of estrogen is more patient compliant as compared to twice a week reservoir patch. Characteristics of drug in adhesive patch may account for improved patient compliance due to ease of remembering once weekly patch application, improved cosmetic acceptance and better adhesion. Examples of marketed preparations of drug-in-adhesives patches are Climara®, Nicotrol® and Deponit®. Design of this system is shown in Figure 4.6.

![Design of drug in adhesive type transdermal patch](image)

**Figure 4.6**: Design of drug in adhesive type transdermal patch

### 4.2.3 Evaluation of transdermal patches

Development of controlled release transdermal dosage form is a complex process involving extensive research. Transdermal patches have been developed to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order to ensure their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage forms and can be classified into following types:

- Physicochemical evaluation
- *In vitro* evaluation
- *In vivo* evaluation

#### 4.2.3.1 Physicochemical Evaluation

**Thickness**: The thickness of transdermal film is determined by traveling microscope (Verma *et al*., 2000), dial gauge, screw gauge (Lewis *et al*., 2006) or micrometer (Aquil *et al*., 2004) at different points of the film.
Uniformity of weight: Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight (Samanta et al., 2003).

Drug content determination: An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution (Costa et al., 1997).

Content uniformity test: 10 patches are selected and content is determined for individual patches. 9 out of 10 patches must have content between 85 to 115% and one not less than 75 to 125% to pass the test of content uniformity. But if 3 patches have 75 to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85 to 115%, then the transdermal patches pass the test.

Moisture content: The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula (Bagyalakshmi et al., 2007).

\[
\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100
\]

Moisture Uptake: Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below (Bagyalakshmi et al., 2007).

\[
\% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100
\]

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness (Mukherjee et al., 2005).
% constriction = \frac{I_1 - I_2}{I_1} \times 100

I_2 = \text{Final length of each strip}
I_1 = \text{Initial length of each strip}

**Folding Endurance**: Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it breaks. The number of times the films could be folded at the same place without breaking is folding endurance value (Ubaidulla et al., 2007).

**Tensile Strength**: To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation (Baichwal, 1985).

\[ \text{Tensile strength} = \frac{F}{a \cdot b} \left( \frac{l + L}{l} \right) \]

F is the force required to break; a is width of film; b is thickness of film; L is length of film; l is elongation of film at break point.

In another study, Tensile strength of the film was determined with the help of texture analyzer (Khan et al., 2000). The force and elongation were measured when the films broke.

**Water vapour transmission studies (WVT)**:

For the determination of WVT, Rao and Diwan, (1997) weighed one gram of calcium chloride and placed it in previously dried empty vials having equal diameter. The polymer films were pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials were accurately weighed and placed in humidity chamber maintained at 68% RH at room temperature. The vials were again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch.
In other reported method, desiccators were used to place vials, in which 200 mL of saturated sodium bromide and saturated potassium chloride solution were placed. The desiccators were tightly closed and humidity inside the desiccator was measured by using hygrometer. The weighed vials were then placed in desiccator and procedure was repeated (Baichwal et al., 1985; Zupan, 1982).

\[ WVT = \frac{W}{ST} \]

W is the increase in weight in 24 h; S is area of film exposed (cm²); T is exposure time

**SEM studies**: Distribution of drug and polymer in the film can be studied using scanning electron microscope. For this study, the sections of each sample are cut and then mounted onto stubs using double sided adhesive tape. The sections are then coated with gold palladium alloy using fine coat ion sputter to render them electrically conductive. Then the sections are examined under scanning electron microscope (Mundargi et al., 2007).

**Adhesive studies**:

The therapeutic performance of TDDS can be affected by the quality of contact between the patch and the skin. The adhesion of a TDDS to the skin is obtained by using PSAs, which are defined as adhesives capable of bonding to surfaces with the application of light pressure. The adhesive properties of a TDDS can be characterized by considering the following factors (Minghetti et al., 2004):

- **Peel Adhesion properties**: It is the force required to remove adhesive coating from test substrate. It is tested by measuring the force required to pull a single coated tape, applied to substrate at 180° angle. The test is passed if there is no residue on the substrate. Minghetti et al., (2003) performed the test with a tensile testing machine Acquati model AG/MC 1 (Aquati, Arese, Italy).

- **Tack properties**: It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer (ASTM 1971; PSTC, 1976; Ho and Doduo, 2007; Dimas et al., 2000).
  - **Thumb tack test**: The force required to remove thumb from adhesive is a measure of tack.
Rolling ball test: This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.

Quick stick (Peel tack) test: The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90° at the speed of 12 inch/min.

Probe tack test: Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.

- Shear strength properties or creep resistance: Shear strength is the measurement of the cohesive strength of an adhesive polymer i.e., device should not slip on application determined by measuring the time it takes to pull an adhesive coated tape off a stainless plate. Minghetti et al., (2003) performed the test with an apparatus which was fabricated according to PSTC-7 (pressure sensitive tape council) specification.

4.2.3.2 In vitro release studies: Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms and hence their in vivo performance (Sood and Panchagnula, 1999). A number of mathematical model have been developed to describe the drug dissolution kinetics from controlled release drug delivery system e.g., Higuchi (Higuchi 1963), First order (Desai et al., 1966), Zero order (Ritschel, 1989) and Peppas and Korsenmeyer model (Korsemeyer and Peppas, 1981; Ritger and Peppas, 1987) (Table 4.5). The dissolution data is fitted to these models and the best fit is obtained to describe the release mechanism of the drug.

There are various methods available for determination of drug release rate of TDDS.

- The Paddle over Disc: (USP apparatus 5 / Ph. Eur. 2.9.4.1) This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32 ±5 °C (Tymes et al., 2006).

- The Cylinder modified USP Basket: (USP apparatus 6 / Ph. Eur. 2.9.4.3) This method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at 32 ±5 °C (Mutalik and Udupa, 2005).
- **The reciprocating disc**: (USP apparatus 7): In this method patches attached to holders are oscillated in small volumes of medium, allowing the apparatus to be useful for systems delivering low concentration of drug. In addition, paddle over extraction cell method (PhEur 2.9.4.2) may be used (Siewert et al., 2003).

- **Diffusion Cells e.g. Franz Diffusion Cell and its modification Keshary-Chien Cell**: In this method, the transdermal system is placed in between receptor and donor compartment of the diffusion cell. The transdermal system faces the receptor compartment in which receptor fluid *i.e.*, buffer is placed. The agitation speed and temperature are kept constant. The whole assembly is kept on a magnetic stirrer and solution in the receiver compartment is constantly and continuously stirred throughout the experiment using magnetic beads. At predetermined time intervals, the receptor fluid is removed for analysis and is replaced with an equal volume of fresh receptor fluid. The concentration of drug is determined spectrophotometrically (Murthy et al., 2001).

The test temperature of dissolution medium is typically set at 32°C (even though the temperature may be higher when skin is covered). Ph. Eur considers 100 rpm a typical agitation rate and also allows for testing an aliquot patch section. The latter may be an appropriate means of attaining sink conditions, provided that cutting a piece of the patch is validated to have no impact on the release mechanism. The dissolution data obtained is fitted to mathematical models in order to ascertain the release mechanism (Siewert et al., 2003).

**Table 4.5**: Different mathematical models for drug release kinetics

<table>
<thead>
<tr>
<th>Model</th>
<th>Method to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero Order</td>
<td>Cumulative amount of drug released versus time</td>
</tr>
<tr>
<td>First Order</td>
<td>Log cumulative percentage of drug remaining versus time</td>
</tr>
<tr>
<td>Higuchi’s model</td>
<td>Cumulative percentage of drug released versus square root of time</td>
</tr>
<tr>
<td>Peppas and Korsmeyer model</td>
<td>Log cumulative percentage of drug released versus log time</td>
</tr>
</tbody>
</table>
In vitro permeation studies: The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages (Elias 1981).

Usually permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as Franz diffusion cell or Keshary-Chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophillic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature (usually 32±0.5°C for skin) and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectrophotometrically. The amount of drug permeated per centimeter square at each time interval is calculated. Design of system, patch size, surface area of skin, thickness of skin and temperature etc. are some variables that may affect the release of drug. So permeation study involves preparation of skin, mounting of skin on permeation cell, setting of experimental conditions like temperature, stirring, sink conditions, withdrawing samples at different time intervals, sample analysis and calculation of flux i.e., drug permeated per cm\(^2\) per second (Lewis et al., 2006; Alam et al., 2009).

Preparation of skin for permeation studies: Hairless animal skin and human cadaver skin are used for permeation studies. Human cadaver skin may be a logical choice as the skin model because the final product will be used in humans, but it is not easily available. Hairless animal skin is generally a favoured alternative as it is easily obtained from animals.

Intact Full thickness skin: Hair on dorsal skin of animal are removed with animal hair clipper, subcutaneous tissue is surgically removed and dermis side is wiped with isopropyl alcohol to remove residual adhering fat. The skin is washed with distilled water. The skin so prepared is wrapped in aluminum foil and stored in a freezer at -20°C till further use. The skin is defrosted at room temperature when required.
Separation of epidermis from full thickness skin: The prepared full thickness skin is treated with 2M sodium bromide solution in water for 6 h. The epidermis is separated by using a cotton swab moistened with distilled water. Then epidermis sheet is cleaned by washing with distilled water and dried under vacuum. Dried sheets are stored in desiccators until further use (Jain et al., 2002; Scott et al., 1986).

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

- Animal models
- Human volunteers

Animal models

Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale (Walker et al., 1983). The most common animal species used for evaluating TDDS are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted lead us to a conclusion that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments (Jeffery and James, 1995). Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in man (Wester and Maibach, 1975).

Human models

The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug (Wester and Maibach, 1982; Jain et al., 2002).
4.2.3.5 Skin irritation studies: White albino rats, mice or white rabbits are used to study any hypersensitivity reaction on the skin by Draize method (Samanta et al., 2003; Ubaidulla et al., 2007). Mutalik and Udupa (2005) carried out skin irritation test using mice. The mice were divided into 5 groups, each group containing 6 animals. On the previous day of the experiment, the hair on the backside area of mice were removed. The animals of group I was served as normal, without any treatment. One group of animals (group II, control) was applied with marketed adhesive tape (official adhesive tape in USP). Transdermal systems (blank and drug loaded) were applied onto nude skin of animals of III and IV groups. A 0.8% v/v aqueous solution of formalin was applied as standard irritant (group V). The animals were applied with new patch/ formalin solution each day up to 7 days and finally the application sites were graded according to a visual scoring scale, always by the same investigator. The erythema was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for scar formation. The edema scale used was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for severe. After visual evaluation of skin irritation, the animals can be sacrificed and skin samples were processed for histological examination.

4.2.3.6 Stability studies: The stability studies are conducted to investigate the influence of temperature and relative humidity on the drug content in different formulations. The transdermal formulations are subjected to stability studies as per ICH guidelines (Panchagnula et al., 2005).

4.3. CURRENT ONGOING RESEARCH

4.3.1 Emerging technologies in transdermal drug delivery

 Until very recently, the only drugs that could permeate transdermally were those possessing a very narrow and specific combination of physicochemical properties. The main limitation of transdermal drug delivery is the lipoidal barrier of stratum corneum. For a drug to be delivered passively via the skin it needs to have adequate lipophilicity and also a molecular weight <500Da. These requirements have limited the number of commercially available products based on transdermal delivery. However, rapid advances in bioengineering have led to the emergence of various new "active" enhancement technologies designed to transiently circumvent the barrier
function of the stratum corneum (Meidan et al., 2004; Sivamani et al., 2007). These novel systems, using iontophoresis, sonophoresis, electroporation, microneedle arrays, RF (radiofrequency) micro channels, pressure waves, or needleless injections will greatly expand the range of drugs that can be delivered transdermally. Crucially, the delivery of macromolecules will become possible and the transdermal flux of other molecules could be enhanced by several orders of magnitude (Aggarwal et al., 2009b).

4.3.1.1. Iontophoresis: To expand the number of compounds that can be delivered via the skin, researchers are developing novel transdermal technologies, including iontophoresis which uses an electric current to cause charged particles to move (Molokhia et al., 2008). A pair of adjacent electrodes placed on the skin set up an electrical potential between the skin and the capillaries below. At the positive electrode, positively charged drug molecules are driven away from the skin’s surface toward the capillaries. Conversely, negatively charged drug molecules would be forced through the skin at the negative electrode. Transdermal iontophoresis has been extensively applied to delivery of anti-inflammatory agents and other compounds for local effects in the context of physical therapy. Iontophoresis has the potential to expand the range of compounds available for transdermal delivery to include proteins and peptides and enhance skin transport. Because the current can be literally switched on and off and modified, iontophoretic delivery enables rapid onset and offset. Hence drug delivery is highly controllable and programmable (Costello and Jeske, 1995; Lopez et al., 2003; Semalthy et al., 2007).

Various companies like Vyteris, based in Fair Lawn, New Jersey, ALZA, General Medical Company of Los Angeles, California and Birch Point Medical in Oakdale, Minnesota are developing iontophoretic delivery systems. Clinical trial results, presented by Vyteris, at the recent “Drug Delivery – Latest Technology & Strategic Partnerships” conference in Munich, Germany, have shown successful delivery of peptides up to a molecular weight of 3,500 Daltons (Prausnitz, 2004).

ALZA has now developed an E-TRANS formulation of fentanyl. In clinical trials, E-TRANS fentanyl administered for 20 minutes every hour for 24 hours resulted in mean serum levels greater than those achieved from intravenous fentanyl. According to ALZA, more than 90% of patients who used E-TRANS indicated they
would like to use the E-TRANS fentanyl system for subsequent surgery, given the convenience, ease-of-use and the ability to achieve pain relief within a few minutes of pressing the button (Guy, 2007). With further advances in formulation science, electrode design and battery technology, iontophoresis may also become a viable alternative for the delivery of other drugs that are used over a long term (Murray et al., 2008).

4.3.1.2. Electroporation: Another transdermal technology being developed is electroporation which involves the creation of aqueous pores in lipid bilayers by the application of a short (microseconds to milliseconds) electric pulse (Prausnitz et al., 1993; Zaharoff et al., 2008). Various parameters governing the performance of electroporative delivery to the skin are voltage, pulse length, number of pulses and electrode area (Sharma et al., 2000). Anionic phospholipids, but not cationic or neutral phospholipids, have been found to enhance the transdermal transport of molecules by electroporation (Sen et al., 2002). Ichor Medical Systems is dedicated to the clinical application and commercialization of electroporation mediated DNA drug delivery (Koch, 2007). Skin electroporation continues to be an active area of research. Larger macromolecules have also been delivered including heparin, insulin and vaccines (Medi et al., 2005; Prausnitz et al., 1995; Widera et al., 2000).

4.3.1.3. RF Microchannels: Radio frequency skin ablation is an established medical technique that has been commonly used for surgical procedures. This technique is modified into RF microchannel technology to create passage through the skin that allows a novel and unique approach for transdermal drug delivery. RF microchannels are a universal solution that can expand the range of molecules that can be delivered transdermally (Levin et al., 2005; Sintov, 2003). The Israeli company, TransPharma Medical, is using alternating current at radio frequencies (RF) to create aquatic throughways, about 100 micrometers wide, across the stratum corneum. TransPharma’s system consists of a reusable, hand-held electronic unit and a disposable microelectrode array consisting of hundreds of closely spaced electrodes. The array is snapped on to the handset and pressed lightly against treatment site. This action activates the handset to apply alternating RF current to the electrodes for several milliseconds, causing microchannels to begin forming. The number of active electrodes determines the number of pores and thus, amongst other factors, the rate at
which drug will cross the skin. When the channels are formed, the current stops automatically, and the user is alerted by audible and visual signals. A closed loop electronic feedback system controls the duration of current delivery by monitoring the current being applied, detecting when the microchannels have reached the desired depth. Importantly, the channels only reach as far as the epidermis, where there are no nerves or blood vessels, and the RF is too high to stimulate muscles or nerves, so there is no significant pain and trauma from the procedure. Following microchannel formation, the electrode array is lifted away from the skin and discarded. The patch containing the drug can then be applied. The microchannels will remain for up to 24 h, allowing for prolonged duration of drug delivery if desired (Levin and Kornfeld, 2007).

4.3.1.4. Ultrasound/sonophoresis: Painless drug delivery: Still another transdermal technology under development is low frequency sonophoresis, which enhances the transport of permeants, such as drugs through cell membranes as a result of ultrasonic energy (Merino et al., 2003). Ultrasonic sound waves cause acoustic cavitation, the resultant effects of which microscopically disrupt the lipid bilayers of the stratum corneum and thereby influencing the influx of permeants. Thus, sonophoresis is able to increase the penetration of various low molecular weight drugs as well as high molecular weight proteins (Sivakumar et al., 2005). Dermisonics is an intellectual property company and advanced technology incubator has patented U-Strip™ system which employs proprietary microelectronics and ultrasonic technologies with a drug-carrying patch to enable the painless delivery of drugs through the skin's natural pores and hair follicles. The U-Strip™ Insulin patch alone could improve the lives of insulin dependent diabetics, reaching 55 million diabetics, or nearly 30% of the total 185 million diabetic population worldwide, who endure painful needle injections to survive this disease (Michael, 2006).

4.3.1.5. Pressure waves: Pressure waves, which are generated by intense laser radiation, can also permeabilize the stratum corneum as well as the cell membrane. These pressure waves are compression waves and thus exclude biological effects induced by cavitations. Their amplitude is in the hundreds of atmospheres (bar) while the duration is in the range of nanoseconds to a few microseconds. The pressure waves interact with cells and tissue in ways that are probably different from those of
ultrasound. Furthermore, the interactions of the pressure waves with tissue are specific and depend on their characteristics, such as peak pressure, rise time and duration. A single pressure wave is sufficient to permeabilize the stratum corneum and allow the transport of macromolecules into the epidermis and dermis. In addition, drugs delivered into the epidermis can enter the vasculature and produce a systemic effect. For example, insulin delivered by pressure waves resulted in reducing the blood glucose level over many hours. The application of pressure waves does not cause any pain or discomfort and the barrier function of the stratum corneum always recovers (Doukas and Kollias, 2004).

4.3.1.6. Microneedles: Recently, the use of micron-scale needles in increasing skin permeability has been proposed and shown to dramatically increase transdermal delivery, especially for macromolecules (Sivamani et al., 2007; Verbaan et al., 2007). Although microneedles were first proposed in 1970s, the technology needed to make microneedles did not become widely available until 1990s. Using the tools of the microelectronics industry, microneedles have been fabricated with a range of sizes, shapes and materials, which create micrometer scale holes in the outer skin layer, thereby allowing passage of large molecules and other compounds that ordinarily could not traverse the skin. Most drug delivery studies have emphasized solid microneedles, which are painless because they are too small to touch the nerves located deeper in the skin. To address practical applications of microneedles, the ratio of microneedle fracture force to skin insertion force (i.e. margin of safety) should be optimal for needles with small tip radius and large wall thickness (Prausnitz et al., 2004). Some scientists recently used this technique to administer insulin to diabetic rats. Over a 4 h time period, blood glucose levels steadily dropped by as much as 80 percent (Martano et al., 2004).

Transdermal delivery using microneedles is also developed by ALZA Corporation and 3M (St. Paul, MN). ALZA’s Macroflux technology uses a thin titanium screen that consists of 200 μm projections that create pathways to deliver the drug through the stratum corneum. Similar to the Macroflux transdermal technology is 3M’s Microstructured Transdermal System (MTS) that also incorporates microneedle technology for targeted delivery of drug molecules across the skin membrane (Chandrashekhar and Shobha, 2006). The drug molecule can be coated onto the micro
projections to achieve a bolus delivery or using a reservoir to ensure continuous delivery of the drug over a specified time (Sivamani et al., 2007). Because people would require minimum training to apply microneedles, these devices may prove useful for immunization programs in developing countries or for mass vaccination or antidote administration in bioterrorism incidents.

4.3.1.7. Needleless injections: This method of administering drugs circumvents issues of safety, fear and pain associated with the use of hypodermic needles. Transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin using a suitable energy source. The mechanism involves forcing compressed gas through the nozzle, with the resultant drug particles entrained within the jet flow reportedly traveling at sufficient velocity for skin penetration (Bremseth and Pass, 2001; Splinter, 2002). The powerjet injector has been reported to successfully deliver testosterone, lidocaine hydrochloride and insulin (Burkoth et al., 1999). Some of the drugs used by the recent transdermal technologies are enlisted in Table 4.6.

4.3.2 Formulation approaches for penetration enhancement of TDDS

Penetration enhancement with special formulation approaches is mainly based on the usage of colloidal carriers. Such carriers include microemulsions, liposomes, ethosomes, complexes, niosomes and prodrugs. These carriers accumulate in stratum corneum or other upper skin layers. Generally, these colloidal carriers are not expected to penetrate into viable skin (Brain et al., 2002; Chein and Lee, 1987; Ranade et al., 1991). Mechanism of action of different carriers is represented in Figure 4.7.

4.3.2.1. Microemulsions: Microemulsions are isotropic, thermodynamically stable solutions in which substantial amounts of two immiscible liquids (i.e. water and oil) are brought into a single phase by means of an appropriate surfactant or surfactant mixture (Safran and Tlusty, 1996).

Penetration enhancement from microemulsions is mainly due to an increase in drug concentration which provides a large concentration gradient from the vehicle to the skin. Furthermore it has been suggested that the surfactants and the oil from the microemulsion interact with the rigid lipid bilayer structure and acts as a chemical enhancer (Schmalfuss et al., 1997). The microemulsions can interact with the stratum
corneum by changing structural rearrangement of its lipid layers and consequently increasing transdermal drug permeation and so act as penetration enhancer (Friberg, 1990). This mechanism can be comparable with saturated and unsaturated fatty acids serving as an oil phase. Other permeation enhancers commonly used in transdermal formulations are oleic acid, isopropyl myristate, isopropyl palmitate, triacetin, isostearyl isostearate, and medium chain triglycerides (Kogan and Garti, 2006).
Chandra et al (2009) used microemulsion-based hydrogel formulation for transdermal delivery of dexamethasone. The optimum formulation consists of various vegetable oils as oil phase, egg lecithin as the surfactant, isopropyl alcohol (IPA) as the co-surfactant, and distilled water as the aqueous phase. The microemulsion-based system was chosen due to its good solubilizing capacity and skin permeation capabilities. Reservoir-type transdermal system was prepared using microemulsion based system. The release studies indicated increased permeation rate with microemulsions in transdermal patch as compared without microemulsions. The pharmacodynamic studies indicated that microemulsion based on nutmeg oil demonstrated a significantly higher anti-inflammatory potential.

4.3.2.2. Liposomes: Liposomes are colloidal particles formed as concentric bimolecular layers that are capable of encapsulating drugs. They are lipid vesicles that fully enclose an aqueous volume. These lipid molecules are usually phospholipids with or without some additives (Vyas et al., 2005). Cholesterol may be included to improve bilayer characteristics of liposomes; increasing micro viscosity of the bilayer, reducing permeability of the membrane to water soluble molecules, stabilizing the membrane and increasing rigidity of the vesicle. There are three types of liposomes: MLV (multilamillar vesicles), SUV (small unilamillar vesicles) and LUV (large unilamillar vesicles) (Barani and Montazer, 2008). Liposomes have already been used to deliver various anti-cancer drugs such as doxorubicin, daunorubicin and camptothecin.

Liposomes can be used as carriers for hydrophilic as well as lipophilic therapeutic agents because of their amphipathic character. They may improve stabilization of unstable drugs by encapsulating them and serve as penetration enhancers facilitating the transport of compounds that otherwise cannot penetrate the skin (De Leeuw et al., 2009). Liposome have higher diffusivity in skin, high biocompatibility, longer release time, greater stability, improved penetration and diffusion properties and controlled degradation. Liposomes may also act as permeation enhancers by penetration of individual lipid components as phospholipids are able to diffuse into the stratum corneum. The interactions and enhancer effects of liposomes on the stratum corneum are based on the lipid mixing of liposomal phospholipids with lipid bilayers of the skin (Kirjavainen et al., 1999). Phospholipids in liposomal systems can disrupt the
bilayer fluidity in the stratum corneum, decreasing the barrier properties of the skin. Moreover, some investigators report that phospholipids in liposomes may mix with the stratum corneum lipids creating a lipid-enriched environment (Valenta et al., 2000). This lipid depot in the skin is preferred by lipophilic drugs, resulting in enhanced skin uptake. Liposome penetration into skin depends greatly on lipid composition, the thermodynamic state of the bilayers and presence of ethanol in the formulation. The key for liposome penetration into skin is the liquid or gel state of the vesicles.

4.3.2.3. Ethosomes: These are liposomes with high alcohol content capable of enhancing penetration to deep tissues and the systemic circulation (Benson, 2005; Dayan and Touitou, 2000; Touitou et al., 2000). It is proposed that alcohol fluidizes the ethosomal lipids and SC bilayer lipids thus allowing the soft, malleable ethosomes to penetrate. Ethosomal formulations contain ethanol in their composition that interacts with lipid molecules in the polar head group regions resulting in an increased fluidity of the stratum corneum lipids. The high alcohol content is also expected to partial extract the stratum corneum lipids. This increases inter and intracellular permeability of ethosomes. The ethanol imparts flexibility to the ethosomal membrane that, facilitate their skin permeation. The interdigitated, malleable ethosome vesicles can forge paths in the disordered stratum corneum, release drug in the deep layers of skin. The transdermal absorption of drugs results from fusion of ethosomes with skin lipids (Godin and Touitou, 2003; Touitou et al., 1997).

Touitou et al. (2000) compared the skin permeation potential of testosterone ethosomes (Testosome) across rabbit pinna skin with marketed transdermal patch of testosterone (Testoderm patch, Alza). They observed nearly 30-times higher skin permeation of testosterone from ethosomal formulation as compared to that marketed formulation. The amount of drug deposited was significantly (p <0.05) higher in case of ethosomal formulation. The AUC and C_max of testosterone significantly improved after application of Testosome as compared to Testoderm. Hence, both in vitro and in vivo studies demonstrated improved skin permeation and bioavailability of testosterone from ethosomal formulation. This group in their further study designs the testosterone non-patch formulation to reduce the area of application (Touitou, 2002).
They have found that with ethosomal testosterone formulation area of application required to produce the effective plasma concentration was 10 times less than required by commercially gel (AndroGel) formulation.

4.3.2.4. Complexes: Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. Cyclodextrins are natural cyclic oligosaccharides that were discovered > 100 years ago, but only some years ago did highly purified cyclodextrins become available as pharmaceutical excipients (Szejtli, 1998; Fromming and Szejtli, 1994). Because of their structure and physico-chemical properties, cyclodextrins as drug carriers have number of advantages like they provide a number of potential sites for chemical modification (Kaneto et al., 1998; Loftsson et al., 1998), they are available with different cavity sizes which makes it possible to entrap drugs of different molecular dimensions, the microenvironment in their cavity is relatively non-polar and lipophilic, they possess low toxicity and low pharmacological activity, they have a good aqueous solubility, they are rather resistant to hydrolysis by organic acids and many common alpha amylases, and completely resistant to yeast fermentation and beta amylases, they are not decomposed by hot alkali, exhibit a high thermal stability, with a decomposition temperature approaching 300 °C, they protect the included /conjugated drugs from biodegradation, they can be used as process aids to remove specific components from a mixture or minerals.

Cyclodextrins enhance drug delivery through aqueous diffusion layers, but not through lipophilic barriers such as the stratum corneum. If the drug release is from an aqueous-based vehicle or if an aqueous diffusion layer at the outer surface of the skin is a rate-determining factor in dermal drug delivery, then cyclodextrins can act as penetration enhancers. However, if drug penetration through the lipophilic stratum corneum is the main rate-determining factor then cyclodextrins are unable to enhance the delivery (Loftsson et al., 2003). Cyclodextrins, by enhancing apparent drug solubility, enhance the drug thermodynamic activity in vehicles and thus cause enhancement of drug release from vehicles. The enhancement of drug release from vehicles by cyclodextrins in turn enhances the dermal drug absorption by improving the drug availability at the lipophilic absorptive barrier surface (i.e. skin) (Matsuda and Arima, 1999; Uekama et al., 1998). Although the drug partition coefficient of
lipophilic drug may be decreased on complexation with hydrophilic cyclodextrins, the increased drug solubility and thermodynamic activity in vehicles can lead to increased drug permeability through skin. This is exemplified by increased skin permeability of dexamethasone by HP-β-CD (Lopez et al., 2000; Williams et al., 1998). The vehicle type used, because of its main influence on the drug’s membrane/vehicle partition coefficient, can markedly affect cyclodextrin-induced enhancement of drug release. Cyclodextrins to be used as excipients in TDDS should possess the following characteristics: they should be therapeutically inert, should not interfere with the normal functions of the skin such as protection from heat, humidity, radiation and other potential insults, should not alter the pH of the skin, should not interact with any component of the skin and should not cause skin irritation.

In TDDS, hydrophilic, hydrophobic as well as ionizable cyclodextrins have already been used as carriers for drugs. Hydrophilic cyclodextrins like 2,6 dimethyl-β-CD and hydroxypropyl-β-CD have been used to improve the solubility and dissolution characteristics of insoluble drugs. Hydrophobic cyclodextrins such as 2,6 diethyl-β-CD have been used to retard the dissolution rate of water soluble drugs and ionizable CDs like carboxymethyl-β-CD, sulfated and sulfobutylether-β-CD have been used to improve inclusion capacity and reduce side effects associated with drugs. The drugs which have been complexed with cyclodextrins successfully in dermal preparation help to minimize systemic side effects, improve patient compliance for long term therapy and increase solubility (Loftsson et al., 1998).

4.3.2.5. Niosomes: Niosomal formulations can increase the amount of drug permeated through the stratum corneum (Van Hal et al., 1996), even if the exact mechanism involved in the drug and/or carrier passage has to be investigated and elucidated in a more detailed way. A hypothetical mechanism of skin penetration is related to a possible reorganization of the niosomal membrane at the level of the stratum corneum (Junginger et al., 1991). In vitro data showed an efficacious transdermal delivery of oestradiol when it was entrapped in C18EO7 and C12EO7 niosomes. The improved drug passage through the outer skin layer seems to be mediated by the high flexibility of the bilayer structure of some niosomal formulations. Similarly, a niosomal formulation made-up of glyceryl dilaurates (C16EO7) and cholesterol also increased the passage through the stratum corneum and the penetration of cyclosporine A into
the inner layer of the skin. Then, niosome can be used as a TDDS for both hydrophobic and hydrophilic drugs.

Niosomes seems an interesting drug delivery system in the treatment of dermatological disorders. Niosomes have also been used in cosmetics and for delivery of peptide drugs. In fact, topically applied niosomes can increase the residence time of drugs in the stratum corneum and epidermis, while reducing the systemic absorption of the drug. They are thought to improve the horny layer properties; both by reducing transepidermal water loss and by increasing smoothness via replenishing lost skin lipids (Manconi et al., 2006). Thus niosomes are able to act as penetration enhancers.

4.3.2.6. Prodrugs: The term prodrug refers to a pharmacologically inactive compound that is converted to an active drug by a metabolic biotransformation which may occur prior, during and after absorption or at specific target sites within the body (Tripathi, 2003). According to IUPAC (International Union of pure and applied chemistry), prodrug is defined as any compound that undergoes biotransformation before exhibiting its pharmacological effects. In recent years numerous prodrugs have been designed and developed to overcome barriers to drug utilization such as low oral absorption properties, lack of site specificity, chemical instability, toxicity, bad taste, bad odor, pain at application site (Verma et al., 2009).

Prodrug has been classified into two types: carrier linked prodrug and bioprecursor. In carrier linked prodrug, the active drug is covalently linked to an inert carrier or transport moiety such as ester and amides. The active drug is released by hydrolytic cleavage either chemically or enzymatically. In bioprecursor, chemical modification of active drug is done but they do not contain a carrier. Such type of prodrug is bioactivated generally by redox biotransformation (Jain, 2001). These prodrugs have been found to improve patient acceptability, alter or improve absorption, alter biodistribution, metabolism and elimination.

The prodrug approach has been investigated to enhance dermal and transdermal delivery of drugs with unfavorable partition coefficients (Sloan, 1992). The factors to be considered which control the penetration kinetics across the skin are the oil-water partition coefficient, lipid solubility, aqueous solubility, molecular size and shape. The prodrug design strategy generally involves addition of a pro-moiety to increase partition coefficient and solubility to increase the transport of the drug in the SC.
Upon reaching the viable epidermis, esterases release the active drug by hydrolysis, thereby optimizing concentration in the epidermis. The intrinsic poor permeability of the very polar 6-mercaptopurine was increased up to 240 times using S-6-acyloxyethyl and 9-dialkylaminomethyl promoieties (Beall and Sloan, 1994) and that of 5-fluorouracil, a polar drug with reasonable skin permeability was increased up to 25 times by forming N-acyl derivatives (Beall and Sloan, 1996; Beall and Sloan, 2002; Bonina et al., 2001; Patrick et al., 1997).

Prodrugs can enhance dermal/transdermal drug delivery via different ways, including increased skin partitioning, increased aqueous solubility, and reduced crystallization. It is also necessary to take care that the delivery system must contain maximum quantity of drug for optimum therapeutic efficacy. Thus the modification of basic drug molecules by chemical methods may improves the physicochemical and biological properties such as partition-coefficient, solubility, pH, absorption, distribution, and ultimately metabolism. The prodrug approach has also been investigated for increasing skin permeability of nonsteroidal anti-inflammatory drugs nalbuphine (Rautio et al., 2000; Sung et al., 2000; Sung et al., 2003). Well established commercial preparations using this approach include steroid esters (e.g. betamethasone-17-valerate), which provide greater topical anti-inflammatory activity than the parent steroids.
Figure 4.7: Mechanism of carriers/vesicles for penetration enhancement (Aggarwal et al., 2010a)
4.4. POTENTIAL OF TRANSDERMAL DELIVERY IN PSYCHIATRIC PATIENTS

In the case of psychotropic drugs, side effects are particularly troublesome and compliance with rigorously regular medication schedules is of great clinical importance for many psychiatric patients. Transdermal drug delivery may be helpful in achieving compliance with a regular medication schedule for certain classes of psychotropic agents. Such classes of psychotropic agents are atypical antipsychotics, where patient non-compliance is always a problem and selective serotonin reuptake inhibitors (e.g. sertaline, paroxetine, fluoxetine, fluvoxamine) and serotonin-norepinephrine reuptake inhibitors (e.g. venlafaxine), which are commonly prescribed for patients with diagnosis of mood disorders, some forms of anxiety disorders, some form of menopausal disorders and eating disorders (especially bulimia nervosa). Certain other psychotropic agents such as carbamazepine and valproic acid, which are used frequently in psychiatric practice as mood stabilizing and antimanic agents, can cause nausea as a gastrointestinal side effect (Murdock et al., 1998). It has been seen that oral administration of lithium, a mood stabilizing agent, is predictably associated with a large number of adverse effects that effects negatively on patient compliance and safety. These events are in turn well related to the pharmacokinetics of orally administered formulations. Symptomatic states related to interdose concentration ‘troughs’ or inadvertent noncompliance further exacerbates noncompliance. The development of sustained or slow release lithium preparations represents a direct response to the limitations of oral routes of lithium salt administration. However the performance of these preparations varies between manufacturers and between batches and they are often used in divided daily dosing strategies similar to nonsustained release preparations. Extremely slow release preparations are furthermore associated with pronounced gastrointestinal irritation. These sustained release preparations represent an imperfect solution to the limitations of oral lithium dosing. Thus there is clinical need for an alternative dosing strategy like transdermal delivery for these drugs that is not met by currently available preparations (Nemeroff and Kilts, 2002).

TDDS of psychotropic drugs like haloperidol, imipramine, fluoxetine, selegiline and lithium have already been studied (Donald et all., 1989; Jain et al., 2002). TDDS of Selegiline, which is a monoamine oxidase inhibitor (MAO), is approved by FDA.
with unique pharmacokinetic and pharmacodynamic properties. This was developed to overcome limitations of orally administered MAO’s, particularly dietary tyramine restrictions and was found to be suitable in long term treatment of major depressive disorder (Goodnick, 2007). It is well known that oral MAOI antidepressants pass through the digestive tract, thus inhibiting intestinal MAO-A, which is needed to break down tyramine (Youdim, 2003), a substance found in certain foods and beverages such as aged cheese and tap beer (Shulman et al., 2001). If a large amount of tyramine is absorbed systemically it can lead to a sudden and large increase in blood pressure called a hypertensive crisis, which is potentially life threatening and requires immediate medical treatment. A few food products may contain large amounts of tyramine that represents a potential risk for patients with significant inhibition of intestinal MAO-A resulting from administration of MAO inhibitors. As a result, patients taking oral MAOIs for major depression are required to avoid foods high in tyramine (Sadock and Sadock, 2000). Through transdermal delivery, selegiline is directly and continuously absorbed into the bloodstream over a 24h period. As a result, initial exposure of the drug to the digestive tract is minimized. It is indicated in animal studies, that transdermal delivery of selegiline (6 mg/24 h patch) allows for levels of medicine to inhibit MAO in the brain thought to be necessary for antidepressant effect while sufficiently preserving MAO-A in the digestive tract to break down tyramine. The data for 6 mg/24 h patch support the recommendation that tyramine dietary modifications are not needed. To reduce the risk of hypertensive crisis, dietary modifications are required with 9 mg/24 h and 12 mg/24 h selegiline transdermal patches (Preskorn, 2006). TDDS of haloperidol, a typical antipsychotic has also been studied and the neuroleptic efficacy of transdermal system was confirmed by maximum graded response in a rotarod apparatus. Minimum extrapyramidal side effects in albino rats were found with a score of zero over a 72 h study. The pharmacokinetic parameters in rabbit model showed a very significant prolongation of action upto 72 h. Thus, transdermal delivery of haloperidol improved the therapeutic profile by preventing the neuroleptic induced extrapyramidal side effects and might be a better alternative during its long period of psychiatric treatment over conventional dosage form (Samanta et al., 2003).
Transdermal patches are also used for treatment of other diseases including neurologic and psychiatric disorders like parkinson disease and attention deficit hyperactivity disease (ADHD). ADHD is the most common psychiatric disorder in children. Currently the most widely prescribed therapy for ADHD is methylphenidate. Methylphenidate has a short plasma half life and thus needs to be frequently administered for effective therapy. Such therapy has limitations in term of patient compliance, particularly in young children (Singh et al., 1999). Innovative research has resulted in development of several formulations of methylphenidate which can modify the delivery of drug in the body. These include modified release preparations like sustained release tablets, controlled release tablets and capsules and transdermal delivery system. The rationale for the development of various delivery systems of methylphenidate stems from the need for drug coverage for at least 8 hours for ADHD patients. This can maintain efficacy over the entire school day and can eliminate the need for repeated administration while the patient is at school (Helen and Mario, 2005). Among these modified drug delivery systems, a methylphenidate transdermal system represents the current status of promising treatment options that may help to shape the future of psychiatric treatment as transdermal patch is convenient to use and can reduce side effects related to oral delivery (Madaan et al., 2006; Sansom, 1999).

Rivastigmine is indicated for treating symptoms of mild to moderate Alzheimer’s disease and dementia in Parkinson’s disease as cholinesterase inhibitor. A rivastigmine patch has been developed which may provide a promising new approach to dementia therapy. It has been found that transdermal delivery of rivastigmine in patients with Alzheimer’s disease significantly reduces the nausea and vomiting commonly associated with oral cholinesterase inhibitor therapy and is as effective as oral therapy. This patch is better tolerated by patients and is preferred by caregivers as it is easier to follow the treatment schedule and it interferes less with daily activities (Oertel et al., 2007). Table 4.7 enlists the psychotropic drugs which are approved by FDA as TDDSs. A list of psychotropic transdermal formulations that are reported in various research publications is shown in Table 4.8.
Table 4.7: FDA approved psychotropic drugs as TDDS (Aggarwal and Dhawan, 2010b)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Application</th>
<th>Company and Approval</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selegiline (Emsam)</td>
<td>Depression</td>
<td>Somerset Pharmaceuticals, Feb. 2006</td>
<td>Holmberg, 2006</td>
</tr>
<tr>
<td>Rivastigmine (Exelon)</td>
<td>Alzheimer disease and Parkinson’s Dementia</td>
<td>Novartis Pharmaceuticals, July, 2007</td>
<td>Yan, 2007</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Attention deficit hyperactive disorder (ADHD)</td>
<td>Noven Pharmaceuticals, April, 2006</td>
<td>Faraone et al., 2007</td>
</tr>
</tbody>
</table>

Table 4.8: Psychotropic drugs studied as transdermal delivery systems

<table>
<thead>
<tr>
<th>Drug</th>
<th>Transdermal drug delivery technology</th>
<th>Category</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Reservoir Patch</td>
<td>Antipsychotic</td>
<td>Selzer, 2004</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Matrix patch</td>
<td>Antipsychotic</td>
<td>Lorenzo et al., 2006</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Matrix Patch</td>
<td>Antianxiety</td>
<td>Powers et al., 1985</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Matrix Patch</td>
<td>Antianxiety</td>
<td>Montenegro et al., 2004</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Gel</td>
<td>Antianxiety</td>
<td>Murdock et al., 1998</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Matrix Patch</td>
<td>Antianxiety</td>
<td>Verma and Iyer, 2000</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Gel</td>
<td>Antidepressant</td>
<td>Ranade, 1991</td>
</tr>
<tr>
<td>Amitryptiline</td>
<td>Gel</td>
<td>Antidepressant</td>
<td>Jain and Panchagnula, 2003</td>
</tr>
<tr>
<td>Selegiline</td>
<td>Reservoir Patch</td>
<td>Antidepressant</td>
<td>Corson, 1993</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Microemulsion</td>
<td>Antidepressant</td>
<td>Laux et al., 2005</td>
</tr>
<tr>
<td>Lithium</td>
<td>Iontophoresis</td>
<td>Antimanic</td>
<td>Nerneroff et al., 2002</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Reservoir Patch</td>
<td>Antidepressant</td>
<td>Midha et al., 2001</td>
</tr>
</tbody>
</table>
4.5. DRUG REVIEW

4.5.1 Risperidone

Risperidone has been developed by Janssen-Cilag. It is a novel antipsychotic with dopaminergic and serotonergic effects. Risperidone is a relatively new antipsychotic available world-wide since the early 1990s. It has been characterized as atypical, but shares some of the extrapyramidal side effect profile of the earlier antipsychotics, particularly at higher doses.

Structure

![Risperidone Structure](image)

- **IUPAC Name**: 3-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl}6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one
- **Molecular formula**: C_{23}H_{27}FN_{4}O_{2}
- **Molecular weight**: 410.485
- **Description**: White or almost white powder
- **Solubility**: 2.8mg/L in water i.e. practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol. It dissolves in dilute acid solutions.
- **Melting point**: 170 °C
- **Storage**: Protect from light.

The main pharmacological activities of risperidone include serotonin 5-HT2 receptor blockade and dopamine D2 antagonism (Megens, 1994). After oral
administration of 1 mg of risperidone 5-HT2 receptor occupancy is about 60% and D2 dopamine receptor occupancy in the striatum is about 50% (Nyberg, 1993). In common with other antipsychotics, risperidone enhances prolactin release, but some central effects such as catalepsy and blockade of motor activity occur at high doses only. Risperidone is 4-10 times less potent than the conventional antipsychotic haloperidol as a central D2 antagonist in rats. Interaction with dopamine D1 receptors occurs only at very high concentrations. The pharmacological profile of risperidone includes interaction with histamine H1 and alpha-adrenergic receptors but the compound does not interact significantly with cholinergic receptors. The drug has good activity against various symptoms and signs associated with schizophrenia (Marder, Davis & Chouinard, 1997). Compared to conventional antipsychotics such as haloperidol, risperidone produces significantly better results according to Positive and Negative Syndrome Scale (PANSS) scores. Marder et al (1997) studied and analysed PANSS scores and produced five dimensions; negative symptoms, positive symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression.

**Clinical Indications**

As far as the manufacturers are concerned risperidone is indicated for acute and chronic schizophrenic psychoses and other psychotic conditions with positive and negative symptoms. It is also indicated for affective symptoms associated with schizophrenia. There is ample evidence of its efficacy (Song, 1997).

There is some evidence that risperidone is useful to some extent in reducing aggression in schizophrenia, although possibly not more effectively than typical antipsychotics (Beck, 1997). There is some evidence for its usefulness as an adjunctive therapy in acute bipolar affective disorder in outpatients and in bipolar disorder when followed up over a six month period (Ghaemi & Sachs, 1997). It has been postulated that there is dopaminergic mediation as well as a serotonergic mediation for some obsessive and related disorders e.g. Tourette's syndrome. Risperidone has therefore also been used to augment SSRIs in obsessive compulsive disorder (Saxena et al, 1996). About 80% patients improved within three weeks of the addition of risperidone. In affective psychoses, risperidone is probably not useful as a single therapeutic agent, that is to say it does not seem to replace an
antipsychotic/antidepressant combination (Muller, 1998). Risperidone has been found useful in adolescent schizophrenia and in children with autistic/pervasive developmental disorders (McDougle, 1997). There has been considerable interest and study of its use in the elderly. There has been documented beneficial use in dementia with persistent voacalisations (Kopala & Honer, 1997), and in demented people with Parkinson’s. There is ample study and anecdotal evidence for the use of risperidone in liaison psychiatry, uses include delirium (Sipahimalani and Masand, 1997), HIV related psychotic disorders (Singh et al, 1997).

Mechanism of action

Risperidone, a benzisoxazole derivative, is a novel antipsychotic drug which binds with high affinity to serotonin type (5-HT$_2$), dopamine type 2 (D$_2$), and $\alpha_1$-adnergic receptors.

Risperidone binds with a lower affinity to the $\alpha_2$-adnergic and histamine H$_1$ receptors. Risperidone does not bind to dopamine D$_1$ receptors and has no affinity (when tested at concentrations $> 10^{-5}$ M) for muscarinic cholinergic receptors. Due to lack of muscarinic receptor binding, risperidone is not expected to produce anticholinergic adverse effects.

Receptors occupancy was also demonstrated in vivo in humans using positron emission tomography, risperidone was shown to block 5-HT$_{2a}$ and dopamine-D$_2$ receptors in three healthy volunteers. Although risperidone is a potent D$_2$ antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy in animal model than classical antipsychotics. Risperidone has also been found to be one of the most potent known antagonist of 5-HT$_{2a}$ (cloned human receptors); 5- HT$_{2a}$ antagonism has been shown to reverse deficits in several in vivo animal models predictive of novel antipsychotic activity (PCP-induced social deficit, microdialysis assessment of dopamine output in prefrontal cortex, glutamate antagonist–induced hyper locomotion). Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side-effects liability.

Pharmacokinetics

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. Steady-state concentration of risperidone and 9-hydroxyrisperidone were reached within 1-2 days and 5-6 days, respectively. In plasma, risperidone is bound to albumin
and alpha\textsubscript{1}-acid glycoprotein. The plasma protein binding of risperidone is approximately 88% that of the metabolite 77%.

Risperidone is extensively metabolized in the liver by CYP2D6 to a major active metabolism, 9-hydroxyrisperidone, which appears approximately equi-effective with risperidone with respect to receptor-binding activity. (A second minor pathway is N-dealkylation). Consequently, the clinical effect of drug is likely to result from the combined concentrations of risperidone and 9-hydroxyrisperidone.

One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In the urine, risperidone plus 9-hydroxyrisperidone represents 35\textendash}45\% of the dose. The remainder is inactive metabolites.

**Adverse effects**

Common side effects include insomnia (about 8\% of patients), weight gain, agitation, anxiety and headache. Less frequent side effects include somnolence, tiredness, dizziness, poor concentration, nausea, and dysfunctions of erection, ejaculation and orgasm.

Orthostatic hypotension can occur particularly initially. Prolactin rises can induce galactorrhoea and gynaecomastia along with disturbances of the menstrual cycle and amenorrhoea. Prolactin rises are also documented in males. Risperidone appears to have less potential for causing EPS than conventional antipsychotics and as such may be more suitable as a maintenance antipsychotic than conventional dopamine-blockers. In a study completed by over two hundred chronic schizophrenic patients by Simpson & Lindenmayer (1997), the severity of EPS in a risperidone treated group as measured by the Extrapyramidal Symptom Rating Scale (ESRS) score did not differ significantly differ from placebo group. There was a linear relationship between mean change scores and increasing risperidone dose on 4 of the 12 ESRS subscales. However, even at 16 mg/day of risperidone, mean change scores were lower than in a group treated with haloperidol group. A linear relationship between increasing risperidone dose and use of antiparkinsonian medications was also apparent. The adverse events also include hypotension (29\%), extrapyramidal effects (11\%), symptomatic orthostasis (10\%), cardiac arrest (1.6\%) with fatality (0.8\%) and delirium (1.6\%). There are several reports of neuroleptic malignant syndrome with risperidone, (Bajjoka et al, 1997). There is at least one recent report associating a
year's exposure to risperidone with tardive dyskinesia, although this was in a patient who had previously been exposed to classical antipsychotics. There have been reports of priapism associated with risperidone (Tekell, Smith & Silva, 1995). There is at least one case report of risperidone causing sudden cardiac death. It is unlikely though that all adverse events are reported, and these probably represent an underestimate of the true incidence. A variant tardive abnormal movement, rabbit syndrome, has also been described with risperidone. Rabbit syndrome is a rare side effect of chronic neuroleptic administration characterized by rapid, fine rhythmic movements of the mouth along a vertical axis. There may be interactions with carbamazepine, which decreases the plasma levels of the antipsychotic fraction of risperidone. Similar drugs that induce hepatic enzymes may have the same effect. Phenothiazines, tricyclic antidepressants, fluoxetine, haloperidol and some beta blockers can increase plasma concentrations of risperidone. No teratogenic effect has been yet noted, but caution should be exercised before prescribing in pregnancy. Risperidone is excreted in milk in animal studies. Women receiving risperidone should not therefore breast feed.

**Dosage and Administration**

**Schizophrenia**

Risperidone can be administered on either a BID or a QD schedule. In early clinical trials, Risperidone was generally administered at 1 mg BID initially, with increase in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg by the third day. Subsequent controlled trials have indicated that total daily risperidone dose of up to 8 mg on a QD regimen are also safe effective. However, regardless of which regimen is employed, in some patient a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increment /decrements of mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of Risperidone. However, maximal effect was generally seen in range of 4 to 8 mg/day. Doses above 6mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with
more extra pyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy result were generally stronger for 8 mg than for 4 mg. The safety of dose above 16mg/day has not been evaluated in clinical trials.

**Bipolar Mania**

**Initial Dose:** Risperidone should be administered on a once daily schedule, starting with 2 mg to 3 mg per day.

**Maintenance Therapy:** There is no body of evidence available for controlled trials to guide a clinician in longer –term management of a patient who requires treatment of an acute manic episode with Risperidone.

**Paediatric Use:** Safety and effectiveness of risperidone in paediatrics patient with schizophrenia or acute mania associated with bipolar I disorder have not been established.

**Dosage Regime**

The drug is available in 0.25, 0.5, 1, 2, 3 and 4 mg tablets.

Risperidone is available in tablet and liquid form. A depot formulation is available (Risperdal Consta®).

**4.5.2 Olanzapine**

Olanzapine is used to treat the manifestations of psychotic disorders such as schizophrenia, hallucinations, delusions, hostility and other bipolar disorder.

**Structure**

![Olanzapine structure](image)

**IUPAC Name:** 2-methyl-4-(4-methyl-1-piperazinyl)-10H[2,3-b][1,5]benzodiazepine

**Molecular formula** : $\text{C}_{17}\text{H}_{20}\text{N}_{4}\text{S}$

**Molecular weight** : 312.43
Description: Yellowish crystalline powder, odourless or almost odourless

Solubility: Practically insoluble in water, sparingly soluble in acetonitrile, ethyl acetate and soluble in chloroform and dichloromethane.

Melting point: 190-195 °C

Storage: Stable under ordinary conditions. It should be protected from light.

Mechanism of Action:

Olanzapine is a thienobenzodiazepine antipsychotic which is thought to work by antagonizing dopamine and serotonin activities. It is a selective monoaminergic antagonist with high affinity binding to serotonin 5-HT2A and 5-HT2C, dopamine D1-4, muscarinic M1-5, histamine H1- and alpha1-adrenergic receptor sites. Olanzapine binds weakly to GABA-A, BZD, and beta-adrenergic receptors.

Pharmacokinetic Profile

Well absorbed, however, 40% of the absorbed drug is metabolized before reaching systemic circulation. It is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. Olanzapine is highly (93%) bound to albumin and alpha1-glycoprotein.

Olanzapine is metabolized primarily through oxidation mediated by cytochrome P450 (CYP) enzymes and by direct glucuronidation. In vitro studies suggest that oxidation is mediated by cytochrome P450 is enzyme IA2 (CYP1A2) and IID6 (CYP2D6), and by flavin containing monoxygenase system. However, studies in subjects who are deficient in CYP2D6 indicate that CYP2D6-mediated metabolism is a minor pathway of olanzapine metabolism.

The two major metabolite, 10-N-glucuronide and 4’-N-desmethyl olanzapine, are not pharmacologically active at the plasma levels achieved during normal therapeutic olanzapine dosing. A study in six patients with clinically significant cirrhosis revealed little effect of hepatic function impairment on the pharmacokinetic of olanzapine. Bioavailability is >57%.

Half-life Elimination: Mean 30 hours; range, 21 to 54 hours; Mean apparent plasma clearance is 25 L/hr; range to 47 L/hr.
Time to peak, plasma: Maximum plasma concentrations after I.M. administration are 5 times higher than maximum plasma concentrations produced by an oral dose.
I.M.: 15-45 minutes
Oral: ~6 hours
Excretion: 40% removed via first pass metabolism; urine (57%, 7% as unchanged drug); feces (30%)
Clearance: 40% increase in olanzapine clearance in smokers. Approximately 57% of an administered dose is renally excreted and 7% as unchanged drug.
Pharmacokinetics of olanzapine is similar in patients with severe renal function impairment and in patients with normal renal function.

**Adverse effects:** Disturbances of body temperature regulation have been associated with use of other antipsychotic agents. Caution is advised in administering olanzapine to patients who will be experiencing conditions that may contribute to an elevation in core body temperature, such as strenuous exercise, exposure to extreme heat or dehydration.

The neuroleptic malignant syndrome (NMS) has been associated with the use of other antipsychotic agents. NMS is potentially fatal symptom complex that may include hyperpyrexia, muscle rigidity, altered mental status and autonomic instability seen as irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia. Elevated creatin kinase, myoglobinuria and acute renal failure also may occur. Differential diagnosis should exclude serious medical illnesses, such as pneumonia or systemic infection presenting in conjunction with extrapyramidal effects, as well as central anticholinergic toxicity, heatstroke, drug fever and primary CNS pathology. The following adverse effects are classified on the basis of their potential clinical significance:

1. **Those indicating need for medical attention:**

**Incidence more frequent:** Agitation, akathesia (restlessness or need to keep moving), extrapyramidal effects, Parkinsonism (difficulty in speaking or swallowing, stiffness of arms or legs, trembling or shaking of hands and fingers), personality disorder (nonaggressive objectionable behaviour).

**Incidence less frequent:** Chest pain, extrapyramidal effects, dystonic (inability to move eyes, muscle spasms of face, neck and back, twitching movements), fever, flu
like symptoms, mood or mental changes including amnesia, anxiety, euphoria, hostility and nervousness, peripheral edema (swelling of feet or ankles) and tardive dyskinesia (lip smacking or puckering, puffing of cheeks, rapid or worm like movements of tongue, uncontrolled chewing movements, uncontrolled movements of arms and legs)

**Incidence rare:** Dyspnea (trouble in breathing), facial edema (swelling of face), menstrual changes, skin rash, water intoxication (confusion, mental or physical sluggishness)

2. **Those indicating need for medical attention only if they continue or are bothersome**

**Incidence more frequent:** Amblyopia, asthenia, constipation, dizziness, drowsiness, dry mouth, headache, increased weight, postural hypotension, rhinitis, tremor.

**Incidence less frequent:** Abdominal pain, articulation impairment (speaking unclearly), hypertonia (tightness of muscles), hypotension (low blood pressure), increased apetite, increased cough, increased salivation (watering of mouth), insomnia (trouble in sleeping), joint pain, nausea, pharyngitis, stuttering, tachycardia, thirst, urinary incontinence (trouble in controlling urine), vomiting, weight loss.

**Incidence rare:** Decreased libido (decrease in sexual desire), diplopia (double vision), palpitation (awareness of heartbeat), photosensitivity (increased sensitivity of skin to sunlight)

**Dosage:**

**Children:** Schizophrenia/bipolar disorder: Oral: Initial: 2.5 mg/day; titrate as necessary to 20 mg/day (0.12-0.29 mg/kg/day)

**Adults:**

Schizophrenia: Oral: Usual starting dose: 5-10 mg once daily; increase to 10 mg once daily within 5-7 days, thereafter adjust by 5-10 mg/day at 1-week intervals, up to a maximum of 20 mg/day; doses of 30-50 mg/day have been used; typical dosage range: 10-30 mg/day

Bipolar mania: Oral:

Monotherapy: Usual starting dose: 10-15 mg once daily; increase by 5 mg/day at intervals of not less than 24 hours; maintenance: 5-20 mg/day; maximum dose: 20 mg/day
Combination therapy (olanzapine in combination with lithium or valproate): Initial: 10 mg once daily; dosing range: 5-20 mg/day

Agitation (acute, associated with bipolar disorder or schizophrenia): I.M.: Initial dose: 5-10 mg (a lower dose of 2.5 mg may be considered when clinical factors warrant); additional doses (2.5-10 mg) may be considered; however, 2-4 hours should be allowed between doses to evaluate response (maximum total daily dose: 30 mg, per manufacturer's recommendation)

**Elderly:** Schizophrenia: Oral: Usual starting dose: 2.5 mg/day, increase as clinically indicated and monitor blood pressure; typical dosage range: 2.5-10 mg/day

**Administration:**

**Injection:** For I.M. administration only; does not administer injection intravenously; inject slowly, deep into muscle. If dizziness and/or drowsiness are noted, patient should remain recumbent until examination indicates postural hypotension and/or bradycardia are not a problem.

**Tablet:** May be administered with or without food/meals.

**Orally-disintegrating tablet:** Remove from foil blister by peeling back (do not push tablet through the foil); place tablet in mouth immediately upon removal; tablet dissolves rapidly in saliva and may be swallowed with or without liquid. It may be administered with or without food/meals.

**Dosage Forms:**

Injection, powder for reconstitution (Zyprexa® IntraMuscular): 10 mg [contains lactose 50 mg]

Tablet (Zyprexa®): 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg

Tablet, orally-disintegrating (Zyprexa® Zydis®): 5 mg [contains phenylalanine 0.34 mg/tablet], 10 mg [contains phenylalanine 0.45 mg/tablet], 15 mg [contains phenylalanine 0.67 mg/tablet], and 20 mg [contains phenylalanine 0.9 mg /tablet].

### 4.6. EXCIPIENTS REVIEW

#### 4.6.1 Eudragits

Eudragit is a copolymer of acrylic and methacrylic acid esters and quaternary ammonium groups. These polymers allow the drug in solid dosage form to perform better during the passage of human body. The flexibility to combine the different
Copolymers enable us to achieve the desired drug release profile by releasing the drug at right place and at right time and over the desired period of time. These polymers also protect the drug from external environment influences and help to enhance patient compliance by masking taste and odour of bitter drugs. Eudragits are also used for enteric coating for targeted drug delivery system and sustained release drug system. Eudragits polymers are available in a wide range of different physical form like aqueous dispersion, organic solution granules and powder.

Figure 4.8: Structure of eudragit

Types of Eudragit and their applications

Poly (meth) acrylate, insoluble but permeable in digestive fluid are Eudragit RL and RS with neutral groups, which enable controlled timed release of drug by pH-independent solution.

Application-Delayed and sustained-release drug delivery can be controlled throughout the entire gastro-intestinal tract to increase therapeutic index and patient compliance. Different polymer combination of Eudragit RL and RS grade help to attained desired drug delivery performance additionally. Eudragit NE and NM grades are neutral ester dispersion which do not require addition of plasticizers, can be used for timed-controlled drug release.

Poly (meth) acrylate, soluble in digestive fluids by salt formation are eudragit S, L, FS and E and these polymers with acidic or alkaline groups enable pH dependent release of drug. They are mainly used for taste masking and for enteric coating. Eudragit L and S polymer are the preferred coating polymers for targeted drug
delivery to the intestine. These Eudragits offer valuable advantage for enteric coating because of:-

1. pH-dependent drug release.
2. Protection of drugs which are sensitive to gastric fluid.
3. Protection of gastric mucosa from aggressive drug.
4. Increase in drug effectiveness.
5. Good storage stability.
6. Gastro-intestinal and colon targeting

These polymers can be combined with other grades of eudragit so as to adjust the dissolution pH and this may help to achieve required drug targeting in GI tract.

Eudragit E-polymers help to seal sensitive drug and increase patient compliance by masking taste and odor.

Eudragit RL 100 and RS 100 are widely used for sustained release, are insoluble, but permeable to the extent depending upon frequency of trimethylammonioethyl ester (TMAE) substitution. Hence RS 100 is less permeable and confers greater sustaining of release than RL 100. Thus mixture of RL and RS polymers shows intermediate water permeability and drug release rates (Melia et al., 1991).

4.6.2 Span 20

Span 20 is sorbitan monolaurate. It is amber, oily liquid, may become hazy or form a precipitate. It has viscosity of 4250 cps. HLB of 8.6, acid no. 7, saponification no. 158-170 and hydroxyl no. 330-358.

It is soluble in methanol or alcohol, dispersible in distilled water and hard water (220ppm), insoluble in hard water (20,000 ppm).

Applications of span 20:

It is used as non-ionic surfactant and as an emulsifying agent in the preparation of water in oil emulsions.

4.6.3 Groundnut oil

Groundnut oil is extracted from the seed of Arachis hypogaea; Family Leguminosae, commonly known as groundnut or peanut or arachis oil. The seed of groundnut fruit commonly contain 40-50% total oil. Groundnut oil is pale in colour.
and of a light consistency. It has a subtle, pleasant flavour and can be heated to a high
temperature.

**Constituents:** Peanut oil has a high content of glycerides of oleic acid, palmitic acid,
linoleic acid, palmitic, arachidic, stearic, lignoceric and other acids.

**Table 4.9:** Properties of groundnut oil

<table>
<thead>
<tr>
<th>Botanical Name:</th>
<th><em>Arachis hypogaeae</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aroma:</strong></td>
<td>Light, nutty</td>
</tr>
<tr>
<td><strong>Properties:</strong></td>
<td>Thick in texture, clear in color, oily feel</td>
</tr>
<tr>
<td><strong>Health Benefits:</strong></td>
<td>Arthritis, Acne, Blackheads</td>
</tr>
</tbody>
</table>

**Uses:** Studies have shown that groundnut oil is just as effective in protecting against
heart disease, as is olive oil. This is because it has similar properties and a similar
fatty acid composition, like olive oil.

### 4.6.4 Olive oil

Olive oil also known as sweet oil or salad oil is fruit oil obtained from the ripe
fruits of *Olea europaea*; family Oleaceae, a traditional tree crop of the Mediterranean
Basin and California. Olive oil is used throughout the world.

**Constituents:** Olive oil is composed mainly of the mixed triglyceride esters of oleic
acid and palmitic acid and of other fatty acids, along with traces of squalene (up to
0.7%) and sterols (about 0.2% phytosterol and tocosterols). The composition varies by
cultivar, region, altitude, time of harvest, and extraction process. Olive oil contains a
group of related natural products with potent antioxidant properties that give extra-
virgin unprocessed olive oil its bitter and pungent taste and are esters of tyrosol and
hydroxytyrosol, including oleocanthal and oleuropein.

**Medicinal use**

Olive oil is unlikely to cause allergic reactions, and as such is used in
preparations for lipophilic drug ingredients. It does have demulcent properties, and
mild laxative properties, acting as a stool softener. It is also used at room temperature
as an ear wax softener. Olive oil is also a potent blocker of intestinal contractions, and
can be used to treat excessive Borborygmus.
Oleocanthal from olive oil is a non-selective inhibitor of cyclooxygenase (COX) similar to classical NSAIDs like ibuprofen. It has been suggested that long-term consumption of small quantities of this compound from olive oil may be responsible in part for the low incidence of heart disease associated with a Mediterranean diet.

Olive oil is also used in soap making and as lamp oil. It is also good for the management of pain. It is also a good natural anti-inflammatory agent. It also makes an excellent lubricant, and can be used in place of machine oil. Some even consider it an aphrodisiac. It helps prevent the appearance of rashes and friction burns, and unless it is rotten it is safe and sterile.

### 4.6.5 Jojoba oil

Jojoba oil is a liquid wax that came into prominence during the 1970s, at the time, when killing of whales for commercial use was banned. Jojoba oil possesses the same properties as the oil derived from the sperm whale. The word Jojoba is pronounced as "ho-ho-ba". Texture wise, Jojoba oil resembles the sebum of our own skin. Jojoba oil makes a superb moisturizer and is suitable for all skin types. It unclogs the pores, thereby making the skin free from any sort of impurities.

Jojoba oil is yellowish in color. The oil extracted from Jojoba (the botanical name of which is *Simmondsia chinensis*) contains adequate amount of myristic acid.

**Uses:** The oil has anti-inflammatory properties. The oil quickly penetrates into the skin and works wonders for dry and sensitive skin. The oil is of great value in getting rid of ugly acne pimples that settle on the skin and become a cause of frustration. Being an antioxidant, it does not become rancid fastly.

In the recent studies, the potential anti-inflammatory activity of jojoba liquid wax (JLW) was evaluated in a number of experimental models. Results showed that JLW caused reduction of carrageenin-induced rat paw oedema in addition to diminishing prostaglandin E2 (PGE2) level in the inflammatory exudates. JLW also caused significant lowering of granulation tissue formation. Topical application of JLW reduced ear oedema induced by croton oil in rats. In the same animal model, JLW also reduced neutrophil infiltration, as indicated by decreased myeloperoxidase activity. In addition, JLW ameliorated histopathological changes affected by croton oil application. In the lipopolysaccharide induced inflammation in air pouch in rats, JLW reduced nitric oxide level and tumor necrosis factor-alpha (TNF-alpha) release.
In conclusion, this study demonstrates the effectiveness of JLW in combating inflammation in several experimental models.

Table 4.10: Properties of olive oil

<table>
<thead>
<tr>
<th>Fat composition</th>
<th>Properties of olive oil</th>
</tr>
</thead>
</table>
| **Saturated fats** | Palmitic acid: 7.5–20.0%  
Stearic acid: 0.5–5.0%  
Arachidic acid: <0.8%  
Behenic acid: <0.3%  
Myristic acid: <0.1%  
Lignoceric acid: <1.0% |
| **Unsaturated fats** | Yes |
| **Monounsaturated fats** | Oleic acid: 55.0–83.0%  
Palmitoleic acid: 0.3–3.5% |
| **Polyunsaturated fats** | Linoleic acid: 3.5–21.0%; Linolenic acid: <1.5% |

**Properties**
- **Food energy per 100g**: 3,700 kJ (880 kcal)
- **Melting point**: –6 °C (21 °F)
- **Boiling point**: 300 °C (572 °F)
- **Smoke point**: 190 °C (374 °F) (virgin); 210 °C (410 °F) (refined)
- **Specific gravity at 20°C**: 0.9150–0.9180 (@ 15.5 °C)
- **Viscosity at 20 °C**: 84 cP
- **Refractive index**: 1.4677–1.4705 (virgin and refined)  
1.4680–1.4707 (pomace)
- **Iodine value**: 75–94 (virgin and refined)  
75–92 (pomace)
- **Acid value**: maximum: 6.6 (refined and pomace); 0.6 (extra-virgin)
- **Saponification value**: 184–196 (virgin and refined); 182–193 (pomace)
- **Peroxide value**: 20 (virgin); 10 (refined and pomace)
### Table 4.11: Properties of jojoba oil

<table>
<thead>
<tr>
<th>Botanical Name:</th>
<th>Simmondsia chinensis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aroma:</td>
<td>Pleasant, light, sweet and nutty</td>
</tr>
<tr>
<td>Properties:</td>
<td>Anti inflammatory, easily absorbable, antioxidant</td>
</tr>
<tr>
<td>Uses:</td>
<td>Hair Care, Skin Care</td>
</tr>
</tbody>
</table>