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Transdermal Delivery Systems

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1.1 Introduction
Among the various routes of drug delivery, oral route is most preferred route to the patient and the clinician alike. Also, formulation of a drug into a delivery system designed for peroral administration e.g., tablet, capsule, etc., has been the traditional way to systemically administer the drugs for over centuries. However, not all the drugs administered by this route exhibit optimal bioavailability either because of the inherent properties of the drug e.g., acid lability or presystemic metabolism or limitations associated with the gastrointestinal tract e.g., chemically hostile environment or the variable absorption characteristics. In some cases the problems associated with the drug can be solved by modifying the formulation e.g., reduction of gastric irritation by application of enteric coating. On the other hand, poor bioavailability associated with the peroral route can often be improved only, by reformulating the drug for delivery \textit{via} a different route such as parenteral route i.e, continuous intravenous infusion. This route at a programmed rate has been recognized as a superior mode of drug delivery not only to bypass the hepatic "first-pass" elimination, but also to maintain a constant, prolonged, and therapeutically-effective drug level in the body. A closely monitored intravenous infusion can provide both the advantages of direct
entry of drug into the systemic circulation and also the control of circulating drug levels. However, such mode of drug delivery entails certain risks and, therefore, necessitates hospitalization of the patients and close medical supervision of the medication. Recently, there is an increasing awareness that the benefits of intravenous drug infusion can be closely duplicated, without its potential hazards, by continuous transdermal drug administration through an intact skin.

In response to this idea, several transdermal drug delivery (TDD) systems have recently been developed aiming to achieve the objective of systemic medication through topical application on the intact skin surface. It is exemplified first with the development of scopolamine releasing TDD system (Transderm-Scop) for 72-hr prophylaxis or treatment of motion-induced nausea, and then by the successful marketing of nitroglycerin-releasing TDD systems (Deponit, Nitrodisc, Nitro-Dur and Transderm-Nitro) as well as isosorbide dinitrate-releasing TDD system (Frondol tape) for once-a-day medication of angina pectoris and clonidine-releasing TDD system (Catapres-TTS) for weekly therapy of hypertension and of estradiol- releasing TDD system (Estraderm) for twice-a-week treatment of postmenopausal symptoms and most recently with the regulatory approval of fentanyl transdermal TDD system.

The present chapter describes fundamentals, types, formulation and evaluation of transdermal drug delivery systems.

1.2 Definition

Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation.

1.2.1 Advantages

1. The drugs from TDDS by pass the hepatic and gastrointestinal metabolism as a result the bioavailability is increased.
2. Risks and inconveniences of intravenous therapy are avoided.
3. Reduced dose frequency and provide predictable and extended duration of action.
4. Reversibility of drug delivery, which would allow the removal of drug source.
5. Greater patient compliance due to elimination of multiple dosing intervals.
6. Enhance therapeutic efficiency by avoiding the peaks and troughs in systemic drug levels associated with conventional delivery.
7. Self-administration is possible.
8. Applicability in geriatric patients as they have impaired memory.

1.2.2 Disadvantages
1. The drug must have some desirable physicochemical properties like lipophilicity, low dose, low molecular weight etc., for penetration through stratum corneum.
2. TDDS are not suitable for drugs that require high plasma levels- e.g., antibiotics.
3. Not suitable for drugs that produce irritation and contact dermatitis.
4. Not suitable for drugs with high molecular weight.
5. Not suitable for drugs that undergo metabolism during the passage through the skin.
6. The transdermal route cannot be employed for a large number of drugs, as the skin is a very efficient barrier for penetration, allowing only small quantities of drug.
7. The barrier nature of the skin changes from one site to another in the same person, from person to person and also with age.

1.3 The Skin
The skin of an average adult human body covers a surface of approximately 2 square meters and receives about one third of the blood circulating through the body. It is one of the most readily accessible organs of the human body with a thickness of only a few millimeters (2.97 ± 0.28 mm). Its major roles are to regulate body temperature, protect tissues from infection, prevent fluid loss, and cushion internal structures. The skin can be divided into three distinct layers: the epidermis, dermis and hypodermis (Figure 1.1). The epidermis is a multilayered structure consisting of cells in various stages of differentiation. The layer that interacts with the environment is the stratum corneum or horny layer. The stratum corneum consists of many layers of compact, flat, dehydrated and keratinized cells. These cells are physiologically inactive and are continuously shed with constant replacement from the underlying viable epidermal tissue.
The stratum corneum has a water content of only 20% as compared to the normal physiological level of 70%, such as in the physiologically active stratum germinativum (which is the regenerative layer of the epidermis). The human skin contains on an average of 10-70 hair follicles and 200-500 sweat ducts per square centimeter. These skin appendages occupy only 0.1% of the total human skin surface. The stratum corneum is the skin’s primary defense layer against invasion and is a composite of corneocytes or terminally differentiated keratinocytes, which are surrounded by crystalline lamellar lipid regions. The corneocytes suspended in this lipid matrix, in addition to the lipid envelope surrounding the cells, form a brick-and-mortar barrier that permits retention of water within the corneocytes in addition to hampering the penetration of foreign particles. The major lipid classes within the stratum corneum are ceramides, cholesterol, and fatty acids. Below the stratum corneum lies the stratum granulosum, or granular layer, followed by the stratum spinosum. The stratum spinosum has an abundance of desmosomes that give a spiny appearance to the cells (prickly layer). The stratum basale, also known as the stratum germinativum, is a single layer of columnar basal cells that are attached to the basement membrane, or basal lamina, via hemidesmosomes. The stratum basale is the regenerative layer composed of undifferentiated keratinocytes and stem cells. As the keratinocytes connected together by desmosomes and gap junctions, mature and migrate through the epidermal layers, they morph from spinous cells to granular cells and finally the flattened corneocytes of the stratum corneum. Along the way the keratinocytes continually gain the protein keratin, and by the time they reach the stratum corneum, they are the fully differentiated cornified cells. The dermis, approximately 2-
3 mm thick, forms the bulk of the skin and is made up primarily of fibroblasts. It consists of a network of collagen tissue fibers with interweaving blood and lymph vessels, sweat and sebaceous glands, hair follicles and nerve endings. The dermis consists of two regions, the papillary, or adventitial that interfaces the basal lamina, and the lower region, the reticular dermis. The reticular dermis make up the bulk of the structural dermis. The lowest layer of the skin is the hypodermis, which is primarily composed of fibroblasts and adipocytes. The hypodermis binds skin to the underlying structures, in addition to serving as a thermo regulator and a cushion to internal organs against trauma.

1.4 Transdermal Delivery Pathways

Transdermal permeation of molecules is believed to occur in two ways: (1) by passively proceeding through the epidermis or (2) by entering a shunt pathway such as a hair follicle or eccrine gland. The Figure 1.2 and 1.3 below depicts these routes with the first and third arrows representing ingress through a sweat gland, the second, transdermal penetration. Shunt pathways only account for approximately 0.1% of the total skin surface, thus passive diffusion has a higher probability of occurring. Molecules with a high molecular weight such as peptides, antibodies and DNA, may require such appendages. Additionally, it is believed that the pilosebaceous unit, which includes the hair follicle, hair shaft and sebaceous gland, might be a highly desirable route for transdermal drug delivery as sebaceous gland cells are more permeable than corneocytes, and the increased blood flow to the hair follicle could enhance systemic drug delivery as well as delivery to the dermis.

For molecules to passively penetrate the epidermis, they can either pass through the corneocytes and lipid matrix in a transeellular route, or by intercellular travel between the corneocytes in the lipid matrix. The latter lipophilic route is the proposed mechanism for most drugs as it is the pathway of least resistance. Lipophilic molecules are better accepted by the stratum corneum. Ideally, a drug must possess both lipoidal and aqueous solubilities. If a drug is too hydrophilic, the molecule will be unable to transfer into the stratum corneum, however if it is too lipophilic, the drug will tend to remain in the stratum corneum layers.
Figure 1.2 Routes of Transdermal Entry (Adopted from Ref 17).

Figure 1.3 Routes of transdermal entry (Adopted from Ref 17).
1.4.1 Factors Affecting Transdermal Permeability

The principal factors influencing transdermal permeability can be classified as follows:

Physico-chemical properties of the penetrant molecule
- Diffusion
- Partition Coefficient
- pH conditions
- Concentration of penetrant molecule

Physico-chemical properties of drug delivery system
- Vehicle
- Composition of drug delivery system

Physiological and pathological conditions of the skin
- Reservoir effect of the horny layer
- Lipid film
- Skin hydration
- Skin temperature
- Regional variation
- Traumatic/pathologic injuries to the skin
- Cutaneous drug metabolism
- Drug metabolism by microorganisms.

1.4.1.1 Physico-chemical properties of penetrant molecule

The salient approaches governing the physico-chemical properties of drug which influence the transdermal permeability include:

1. Drug transport within the delivery system to the device-skin surface interface.
2. Partitioning of drug across the stratum corneum
3. Diffusion of drug across the stratum corneum
4. Drug partitioning from the stratum corneum to the viable epidermis.
5. Transport of drug through the viable tissue.
6. Drug uptake by the cutaneous microcapillary network and subsequent systemic distribution
Diffusion

The transport characteristics of the drug are determined primarily by its size and by its level of interaction with the media through which diffusion is takes place, i.e., delivery system, stratum corneum, viable epidermis. Most drugs in current use have molecular weight less than 1000 daltons. Beyond this magnitude, organic molecules tend to fall into categories such as polymers or peptides. The drugs having molecular weight less than 500 daltons have been widely accepted for transdermal patches for reasons of better diffusion characteristics. For small species (<1000 daltons) the effect of size on diffusion in liquids may be viewed in terms of the Stokes’-Einstein equation, i.e., \( D = C \cdot M^{-1/3} \), where \( M \) = molecular weight, \( C \) = constant, \( D \) = diffusion.

Partition Coefficient

Drug possessing both water and lipid solubilities are favorably absorbed through the skin. A lipid/water partition coefficient of 1 or greater is generally required for optimal transdermal permeability. In percutaneous absorption there are two key partitioning processes, between the delivery system and stratum corneum and between the lipophilic stratum corneum and the aqueous epidermis with time. The molecules must favor the stratum corneum while striking a balance between stratum corneum and viable dermal tissue so as to have entry to systemic circulation.

The partition coefficient of a drug molecule may be altered by chemical modification of its functional groups. Membrane partition coefficient increases exponentially as the length of the lipophilic alkyl chain increases.

pH condition

Application of solutions whose pH values are very high or very low can be destructive to the skin. With moderate pH values, the flux of the ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability.

Concentration of penetrant molecule

The amount of drug percutaneously absorbed per unit surface area per unit time interval increase as the concentration of the drug in the vehicle is increased. Assuming membrane limited transport, increasing concentration of dissolved drug causes a proper increase in flux. At concentration higher than the solubility, excess solid drug functions as a reservoir and helps to maintain a constant drug concentration for a prolonged period of time.
1.4.1.2 Physico chemical properties of drug delivery systems

Generally in the drug delivery systems, vehicles do not increase the rate of penetration of a drug into the body but serves as carriers for the drug.

**Vehicle**

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

- Whether the drug molecules are dissolved or suspended in the delivery system, the interfacial partition coefficient of drug from the system to skin tissue. Lipophilic solvent vehicles facilitate penetration
- The pH of the vehicle can influence the rate of release of the drug from the delivery system since the thermodynamic activity of acidic and basic drugs is affected by the pH.

**Composition of drug delivery system**

It affects not only the rate of drug release but also the permeability of stratum corneum by means of hydration, mixing with skin lipids or other sorption promoting effects.

1.4.1.3 Physiological and pathological conditions of the skin

The various physiological and pathological parameters of skin and related barrier functions include:

- Pathophysiological nature of the skin
  - Reservoir effect of the Horny layer
  - Lipid film on skin surface
  - Hydration of stratum corneum

- Environmental factors
  - Temperature
  - Humidity

- General subject factors
  - Race
  - Age
  - Gender
Anatomical site
General health of subject
Disease and trauma

Factors associated with skin conditioning
Bathing/Cosmetic habits

Reservoir effect of the horny layer
The reservoir effect is due to the irreversible binding of a part of the applied drug with the skin. This binding can be reduced by the pretreatment of the skin surface with anionic surfactant.

Lipid film
This acts as a protective layer to prevent the removal of moisture from the skin and helps in maintaining the basic function of stratum corneum. Defatting of this film was found to decrease transdermal absorption.

Hydration of stratum corneum
Hydration results from water diffusion from underlying epidermal layers or from accumulating perspiration after application of an occlusive vehicle or covering on the surface under occlusive conditions. Occlusion also reduces the ‘irreversible’ binding capacity of the stratum corneum. When the skin undergoes hydration, its resistance and capacitance may change. As the time of hydration increases, the low frequency impedance of the excised skin decreases with time. A much less activation energy is required to diffuse through hydrated skin.

Temperature
Raising skin temperature results in an increase in the rate of skin permeation. This may be due to (i) thermal energy required diffusivity (ii) solubility of drug in the skin tissues and (iii) increased vasodilation of skin vessels.

Humidity
Humidity has been directly related to skin permeability by its effect on insensible perspiration. Hummerlaud et. al.²⁰ studied transdermal water loss in newborn infants as a function of relative humidity and the body site of the infant, which indicated a linear relationship between evaporation rate and humidity at constant ambient temperature. Similar studies have verified that the driving force for passive diffusion of water through skin is reduced in proportion to the degree of moisture in the ambient air.
Race

Striking differences in skin coloration exist across races of the man, which relates to nature, numbers, geometrics and distribution of melanin pigment granules deposited in the epidermis by melanocytes. The most striking evidence that there are racially derived permeability differences in the cutaneous barrier is provided by Weighand et. al. They found that Caucasians reacted more strongly to irritants than Negroes when the respective skin was intact. On stripped skin however the responses were equivalent.

Age

Fetal and infant skin appears to be more permeable than adult skin. The stratum corneum of preterm infants is not well developed and as such provides, little barrier to the ingress of substances. So this route of delivery is possible for neonatal therapy when difficulty is encountered in oral or intravenous administration. There appear good reasons to suspect that percutaneous absorption does change with age. It is known that the aged stratum corneum is considerably dryer than the young adult horny layer and that it contains lower lipid content. A reduced presence of water implies that aged skin provides a less attractive environment to less lipophilic moieties. The diminished lipid content provides a reduced dissolution medium for chemicals administered to skin surface. Thus probing the barrier function at both macroscopic & molecular levels as a function of age is now realistic.

Gender

Though there are striking differences in the general appearances of the skin and the distribution and prominence of hair between post adolescent males and females, there is no convincing evidence to suggest that anatomical dissimilarities have much bearing on the barrier function of the tissue. The essential need for protection from water loss, which does not differ between the sexes, seems to impart qualities to the skin, which determine its membrane function more than any other factor.

Anatomical site

Differences in the nature and thickness of the barrier layer of the skin cause variation in permeability. Based on the Scheuplein and Blank compilation, the diffusion of water through adult skin increases in the order: back, abdomen and forearm<back of hand<forehead<palm, sole & scrotum.
1.4.2 Strategies for the Enhancement of Transdermal Permeation

1.4.2.1 General aspects

Development process of transdermal system can be divided into four stages in which different studies are carried out. These include feasibility studies, formulation studies, patch optimization and clinical studies. Feasibility studies are carried out to determine the permeability of the selected drugs across the skin to assess whether the drug can permeate skin in adequate quantity to show its therapeutic effect. For this purpose \textit{in vitro} skin permeation studies are performed. Once the feasibility of the drug is established, the drug needs to be formulated in a stable and marketable formulation. Various excipients are selected and incorporated in the formulation. After that, various formulation studies like drug excipient compatibility, formulation stability and skin irritation studies are carried out. Design of drug delivery system is decided and the formulation is converted into a patch to get a transdermal system. Various types of backing membrane, rate controlling membrane and adhesives are tested to achieve desired efficacy. The marketing aspects are also considered in the selection of shape, size and appearance of the delivery system. In the clinical phase, various aspects of transdermal drug delivery including surface area, effect of penetration enhancer, different types of release mechanisms are considered.

If the drugs under study have not no great ability to cross the skin, ways must be found to modify the diffusional barrier or to increase drug permeation by another way. Passive permeation across the stratum corneum is especially difficult to compounds, which are hydrophilic (log Pret < 1), very lipophilic (log Pret > 3), of high molecular weight (MW > 400 g/mol) or charged.

Generally, methods to enhance transdermal drug permeation can be grouped into two categories: physical methods and chemical methods.

Chemical enhancers and prodrugs have been found to increase transdermal drug transport via several different mechanisms, including increased solubility of the drug in the donor formulation, increased drug partitioning into the stratum corneum, fluidization of the lipid bilayers, and disruption of the intracellular proteins. It is obvious that many different groups of chemicals have the potential to alter the barrier properties of skin.
The prodrugs are pharmacologically inactive drug molecules, which require a chemical or enzymatic transformation to release the active parent molecule. Prodrugs have been used to improve the delivery of drugs across the skin, because a lot of nonspecific esterases and other enzymatic activities are present in the epidermis. However, high prodrug concentration in the skin may lead to enzyme saturation, which hinders the conversion of a prodrug into an active drug molecule.

1.4.2.2 Physical methods

These methods have been tested to create effective transdermal drug delivery.  

Phonophoresis or Sonophoresis

Enhancement of migration of drug molecules through the skin by ultrasonic energy. These acoustic waves used in the frequency range from 20 KHz to 20 MHz are known to interact with tissue through several physical phenomena like refraction, transmission, absorption, scattering etc., and causes disruption of stratum corneum. Following disruption, stratum corneum restores its original configuration rapidly; however it was observed that some foreign molecules and bacteria may also penetrate along with the drug molecules. Drugs like immunosuppressants, steroids, anti-inflammatory agents, analgesics, local anaesthetics, proteins (insulin), antiviral (interferons), antibodies etc, are tested.

Iontophoresis

Iontophoresis is a noninvasive and painless means of delivering various drugs into the body. Transdermal administration of drugs through the skin is assisted by electrical energy in the iontophoretic method. Iontophoresis concerns small amounts of physiologically acceptable electric current to drive charged drug molecules into the body using an electrode with the same charge of the drug, producing electrostatic repulsion. Skin is a permselective membrane with negative charge at physiological pH of 7.4. So the counterions are usually cations and electro-osmotic flow occurs (causing a net convective flow) from anode to cathode, thus enhancing the flux of positively charged drugs. Currently the US military is trying to develop a wristwatch sized iontophoresis device that will enable monitoring of the conditions of the soldiers in the
battlefield from the satellite, and deliver the required drugs and vitamins etc, by a signal sent to the device\textsuperscript{34}. Figure 1.4 shows a typical iontophoretic system.

![Figure 1.4](image)

**Figure 1.4** Iontophoretic delivery system 2. Electrode system applied to the skin surface.

**Electroporation**

Electroporation involves the creation of transient aqueous pathways in the lipid bilayer membrane by the application of a short electric field pulse\textsuperscript{35}. Two main pulse protocols have been employed to promote transport; intermittent application of short high-voltage pulses (about 1 ms and 100 V across the skin) and a few applications of long medium-voltage pulses (about 100 ms and > 30 V across the skin)\textsuperscript{37}. The exact mechanism of access by electroporation remains unknown, it has been successfully applied for the transfection of DNA and macromolecules such as peptides, proteins, and other gene-based compounds\textsuperscript{34}. Use of electroporation has been suggested for cancer chemotherapy, delivery of peptides, polysaccharides, oligonucleotides, and genes\textsuperscript{38}.

**Jet injectors**

Jet injectors use brute force to deliver therapeutic moieties through the skin. There are wide ranges of delivery devices like gene-guns, which propel DNA coated gold beads through the skin by helium.

**Microneedles**

Microfabricated needles approximately 150 μm long were able to increase the permeability of the human skin. These arrays of micro needles create conduits across stratum corneum potentially allowing the transport of drug molecules. This technology provides hope for an effective transdermal system for the delivery of macromolecules.
1.4.2.3 Chemical penetration enhancers

Essential oils, terpenes and terpenoids

Terpenes are found in essential oils, and are compounds comprising only carbon, hydrogen and oxygen atoms, yet which are not aromatic. Numerous terpenes have long been used as medicines, flavors and fragrance agents. For example, menthol is traditionally used in inhalation pharmaceuticals and has a mild antipruritic effect when incorporated into emollient preparations. It is also used as a fragrance and to flavor tooth pastes, peppermint sweets and menthylated cigarettes. The essential oils of eucalyptus, chenopodium and ylang were effective penetration enhancers for 5-flourouracil traversing in human skin \textit{in vivo}\textsuperscript{39}. The most potent of these essential oils, eucalyptus increased the permeability coefficient of the drug 34-fold. The principal terpene element within eucalyptus oil is 1,8-cineole and terpenoids were evaluated as enhancers for the model hydrophilic drug 5-flourouracil in human skin \textit{in vitro}\textsuperscript{41}. Another terpene, d-limonene is effective as permeation enhancer for the permeation of lipophilic molecules, indomethacin and nitrendipine etc\textsuperscript{41}.

1.4.3 Basic components of Transdermal Drug Delivery Systems

1.4.3.1 Drug

\textbf{Physicochemical properties of Drug:} M.W < 1000 Daltons, affinity for both lipophilic and hydrophilic phases; M.P < 200 °C

\textbf{Biological properties of drug:} Potent (Dose should be few mg/day); short biological half life (t$_{1/2}$); free from cutaneous irritancy or allergic response; which degrade in the GI tract/ inactivated by hepatic first-pass effect; tolerance must not develop under the near zero-order release profile; long term administration for a long period of time by other routes. E.g., nitrendipine, carvedilol, buspirone, diltiazem and domperidone etc.

1.4.3.2 Polymer

Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and released through it. The properties of polymer include; should be stable, non-reactive with drug; easily manufactured and fabricated into the desired product; inexpensive; polymer and its degradation products must be non-toxic or non-antagonistic to the host. Mechanical properties of the polymer should not deteriorate excessively when large amount of active agent is incorporated.
Natural Polymers: Cellulose derivatives, shellac, waxes, gums and their derivatives etc.

Synthetic Elastomers: Polybutadiene, hydrii rubber, polysiloxane, silicone rubber, nitrile, acrylonitrile, butyl rubber, styrene butadiene rubber, neoprene etc.

Synthetic Polymers: Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinyl pyrrolidone and polymethyl methacrylate etc.

1.4.3.3 Permeation enhancers

Solvents: Solvents act by increasing penetration possibly by swelling the polar pathway and/or by fluidizing lipids. E.g., Ethanol; DMSO; DMF; N-methyl-2-pyrrolidone; Laurocapram (Azone), PG; IPM.

Surfactants: Sodium lauryl sulfate, Decodecylmethyl sulphoxide Pluronic F127, Pluronic F68, etc., Sodium taurocholate, Sodium deoxycholate and Sodium-tauroglycocholate

1.4.3.4 Other excipients

Adhesives

Polyisobutylenes: Polyisobutylene (PIB) are elastomeric polymers that are commonly used in PSAs, both as primary-base polymers and as tackifiers. They are homopolymers of isobutylene and feature a regular structure of a carbon–hydrogen backbone with only terminal unsaturation. This molecular structure leads to chemical inertness and good resistance to weathering, ageing, heat and chemicals. Their stability, inertness and broad acceptance in FDA-regulated applications means that PIBs are a good candidate adhesive for use in TDD devices. These are highly paraffinic and non-polar substances, soluble in typical aliphatic and aromatic hydrocarbon solvents, but not in common alcohols, esters, ketones and other oxygenated solvents. The water permeability is related to the higher the molecular weight and is decreased with increasing molecular weight. Therefore, PIBs are preferred for use with drugs with a low solubility parameter and low polarity. The low molecular weight PIBs are very viscous, soft and tacky semi-liquids, whereas the high molecular weight grades are tough and elastic rubbery solids. The low molecular weight polymers are primarily used as tackifiers to provide tack to the high molecular weight PIBs or other adhesive polymers. The high molecular weight PIBs are used to impart internal strength and flow...
resistance of PSAs. Examples of tackifiers include low molecular weight polybutenes, rosin ester resins, hydrocarbon resins and polyterpenes.

**Silicones**

Silicone PSAs have been used in medical and healthcare devices since the 1950s. Their biocompatibility has been established through a history of many years of safe usage, and their application in various medical devices, and their chemical and physiological inertness. Silicone PSA formulations are based on two major components: a polysiloxane (silicone) polymer and a silicate resin (Figure 1.5). The polymer is a high molecular weight polydimethylsiloxane that contains residual silanol functionality (SiH3OH) on the ends of the polymer chains. The resin is a three-dimensional trimethylsiloxy and hydroxyl end-blocked silicate structure. The silicone polymer and silicate resin are dissolved together in a nonpolar hydrocarbon solvent (such as xylene and hexane).

![Silicone Pressure-Sensitive Adhesives (PSAs)](image)

**Figure 1.5** Silicone pressure-sensitive adhesives (PSAs).
During processing, a condensation reaction takes place between the silicone polymer and the silicate resin. This condensation results in a network of polymer chains that are cross linked with the resin molecules. The final silicone PSA formulation is a one component system, unlike the PIB-based PSA formulations, which are merely a physical blend of a high molecular base polymer and a low molecular weight polymer or tackifying resin. The ratio of resin to polymer is used to produce PSAs with a wide range of adhesive properties. Increasing the polymer content provides a softer and tackier adhesive, whereas higher resin levels produce an adhesive with a lower tack but higher adhesion and resistance to cold flow. The other important factor that controls the adhesive properties is the level of silanol functionality present in the final polymer and resin formulation. Polydimethylsiloxanes have a unique molecular structure in which an inorganic silica-like backbone (-Si-O-Si-) supports a regular arrangement of pendant methyl groups. This structure enables silicone PSAs to have a high permeability to vapor, gases and a wide variety of therapeutic molecules.

Silicone adhesives are supplied as two types of pre-formulated products. The regular type contains residual silanol, and the amine compatible type has the reactive silanols end-capped. To improve cohesive strength, reinforcing fillers, such as finely divided silica, can be incorporated into the silicone PSA formulation. Water-soluble additives such as ethylene glycol, glycerin, and polyethylene glycols were used to control the water sorption into the silicone polymer matrix and to enhance the release of drugs. Another method of controlling the release of active agents is to manage the degree of cross linking in the silicone polymer matrix. Cross linking will improve cohesive strength with a corresponding decrease in tack, adhesion and drug release properties.

Pressure sensitive adhesives include polyisobutylanes, acrylics and silicones.

**Backing membrane**

Metallic plastic laminate, plastic backing with absorbent pad; occlusive base plate (aluminium foil); adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil) etc.
Table 1.1 Backing membranes used in TDDS.

<table>
<thead>
<tr>
<th>Product</th>
<th>Polymer</th>
<th>Oxygen Transmission (Cm³/m²/24h)</th>
<th>MVTR (g/m²/24h)</th>
<th>Enhancer Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co trans 9702, Co trans 9706</td>
<td>EVA</td>
<td></td>
<td>52.8</td>
<td>Medium</td>
</tr>
<tr>
<td>Co trans 9720, 9722</td>
<td>PE</td>
<td>2950</td>
<td>9.4</td>
<td>Medium</td>
</tr>
<tr>
<td>Foam tape 9772L</td>
<td>PVC foam</td>
<td></td>
<td>450</td>
<td>-</td>
</tr>
<tr>
<td>Foam tape 9773</td>
<td>Polyolefin foam</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Scotchpak 1006</td>
<td>PE, Aj vapor coat, ET, EVA</td>
<td>4.6</td>
<td>0.3</td>
<td>High-PET side</td>
</tr>
<tr>
<td>Scotchpak 1109</td>
<td>PE, Aj vapor coat, PET</td>
<td>4.6</td>
<td>0.3</td>
<td>High</td>
</tr>
<tr>
<td>Scotchpak 9723</td>
<td>PE, PET laminate</td>
<td>100</td>
<td>12</td>
<td>High-PET side</td>
</tr>
<tr>
<td>Scotchpak9732, 9733</td>
<td>PET, EVA laminate</td>
<td>80</td>
<td>80</td>
<td>High-PET side</td>
</tr>
</tbody>
</table>

PE-Polyethylene; PVC-Polyvinyl chloride; EVA-Ethylene vinyl acetate; MVTR-Moisture-vapor transmission rate; PP-polypropylene; PU-Polyurethane; PET-Poly(ethylene terephthalate)(polyester)

Table 1.2 Methods to enhance transdermal permeability of (macromolecular) drugs.

<table>
<thead>
<tr>
<th>Method</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical enhancers</td>
<td>Compromization of the tightly structured stratum corneum lipid bilayers</td>
</tr>
<tr>
<td>Lipid vesicles</td>
<td>Cumulation of drugs in the stratum corneum</td>
</tr>
<tr>
<td>Iontophoresis</td>
<td>Low current/voltage electrostatic repulsion, electroosmosis</td>
</tr>
<tr>
<td>Low-frequency ultrasound</td>
<td>Local thermal effect, weakened bilayers of the stratum corneum by cavitation</td>
</tr>
<tr>
<td>Electroporation</td>
<td>High voltage short term electrical pulses</td>
</tr>
<tr>
<td>(Micro) needles</td>
<td>Transient holes in the skin</td>
</tr>
<tr>
<td></td>
<td>Invasive “gene guns”</td>
</tr>
</tbody>
</table>
Figure 1.6 Actions of penetration enhancers within the intercellular lipid domain (Adopted from Ref 44; Corss Ref 45).

1.5 Types of Transdermal Drug Delivery Systems

1.5.1 Reservoir system

The reservoir system is fabricated by embedding (sandwiching) drug reservoir between an impervious backing layer and a rate controlling membrane (Figure 1.7a). The drug releases only through the rate-controlling membrane, which can be microporous or nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. On the outer surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic adhesive polymer can be applied. Eg., Transderm-Nitro and Transderm-Scop.
1.5.2 Matrix systems-drug-in-adhesive system

The drug reservoir is formed by dissolving or dispersing the drug in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in the case of hot-melt adhesives) onto an impervious backing layer (Figure 1.7b). On top of the reservoir, layers of unmedicated adhesive polymer are applied. Eg., Isosorbide dinitrate releasing transdermal therapeutic system (Frandol tape).

1.5.3 Matrix-dispersion system

The drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is then fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing layer (Figure 1.7c). Instead of applying the adhesive on the face of the drug reservoir, it is spread along the circumference to form a strip of adhesive rim. Eg., Nitro-Dur.

1.5.4 Micro reservoir systems

This drug delivery system is a combination of reservoir and matrix-dispersion systems. The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unleachable, microscopic spheres of drug reservoirs (Figure 1.7d). The thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ. Eg. Nitrodisc.
Figure 1.7 Showing different types of TDDS.
Table 1.3  Transdermal Delivery Systems in World Market.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Manufacturer</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>Nicotinell®</td>
<td>Novartis</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Matrifen®</td>
<td>Nycomed</td>
<td>Pain relief patch</td>
</tr>
<tr>
<td>Norelgestromin/</td>
<td>Ortho Evra®</td>
<td>ORTHO MC NEIL</td>
<td>Postmenstrual syndrome</td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac diethyl amine</td>
<td>Nupatch 100</td>
<td>Zydus Cadilla</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>Neupro®</td>
<td>UCB &amp; Schwarz</td>
<td>Early stage idiopathic Parkinson’s disease</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Alora</td>
<td>Thera Tech/ Proctol and Gamble</td>
<td>Postmenstrual syndrome</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Nicoderm®</td>
<td>Alza/ GlaxoSmithKline</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Estraderm</td>
<td>Alza/ Novartis</td>
<td>Postmenstrual syndrome</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Climara</td>
<td>3M Pharmaceuticals/ Berlex labs</td>
<td>Postmenstrual syndrome</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Androderm</td>
<td>TheraTech/ GlaxoSmithKline</td>
<td>Hypogonadism in males</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Nitrodisc</td>
<td>Robert Pharmaceuticals</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Transderm-Scop</td>
<td>Alza/ Novartis</td>
<td>Motion sickness</td>
</tr>
<tr>
<td>Estrogen/ Progesterone</td>
<td>Nuvelle TS</td>
<td>Ethicalholdings/ Schering</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Deponit</td>
<td>Schwarz pharma</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Nitro- dur</td>
<td>Key pharmaceuticals</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Catapress TTS</td>
<td>Alza/ Boheinger</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Fem patch</td>
<td>Parke- Davis</td>
<td>Postmenstrual syndrome</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Minitran</td>
<td>3M Pharmaceuticals</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Duragesic</td>
<td>Alza/Janssen pharmaceuticals</td>
<td>Moderate/ severe pain</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Transderm-Nitro</td>
<td>Alza/ Novartis</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Testoderm TTS</td>
<td>Alza</td>
<td>Hypogonadism In males</td>
</tr>
<tr>
<td>Oxybutinin</td>
<td>Oxytrol</td>
<td>Watson Pharma</td>
<td>Overactive bladder</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Prostep</td>
<td>Elan Corp/ Leder labs</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Lidoderm</td>
<td>Teikoku Pharma</td>
<td>Pain of post-herpetic neuralgia (shingles pain)</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Exelon</td>
<td>Novartis</td>
<td>Parkinsonism</td>
</tr>
<tr>
<td>Product</td>
<td>System type</td>
<td>Backing layer</td>
<td>Drug reservoir</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>------------------------------------</td>
<td>--------------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td><strong>Testoderm-TTS (non scrotal) (Testosterone)</strong></td>
<td>Membrane-controlled TTS</td>
<td>Transparent polymer, EVA copolymer</td>
<td>Hydroxypropyl cellulose, ethanol, testosterone</td>
</tr>
<tr>
<td><strong>Testoderm-TTS</strong></td>
<td>Matrix, stripped adhesive</td>
<td>Polyester</td>
<td>EVA copolymer, testosterone</td>
</tr>
<tr>
<td><strong>Testoderm with adhesive (scrotal) (Testosterone)</strong></td>
<td>Matrix, stripped adhesive</td>
<td>Polyester</td>
<td>EVA copolymer, testosterone</td>
</tr>
<tr>
<td><strong>Transderm Scop (Scopolamine)</strong></td>
<td>Membrane controlled</td>
<td>Tan-colored polyethylene, aluminized polyester, EVA co-polymer</td>
<td>PIB, mineral oil, scopolamine</td>
</tr>
<tr>
<td><strong>Transderm-Nitro/Transderm-Nitro (Nitroglycerin)</strong></td>
<td>Membrane controlled</td>
<td>Tan-colored polyethylene, aluminized polyester, EVA co-polymer</td>
<td>Silicone fluid, nitroglycerin, lactose triturate</td>
</tr>
</tbody>
</table>

Table 1.4 Contd…
<table>
<thead>
<tr>
<th>Product</th>
<th>System type</th>
<th>Backing layer</th>
<th>Drug reservoir</th>
<th>Rate Controlling membrane</th>
<th>Adhesive</th>
<th>Peelable liner</th>
</tr>
</thead>
<tbody>
<tr>
<td>NicoDerm CQ/NiQuitin CQ (Nicotine)</td>
<td>Membrane-controlled</td>
<td>Tan-colored polyethylene, aluminized polyester, EVA co polymer, or transparent polyester, EVA copolymer</td>
<td>EVA copolymer, nicotine</td>
<td>Polyethylene</td>
<td>PIB</td>
<td>Silicone coated polyester</td>
</tr>
<tr>
<td>Duragesic / Durogesic (Fentanyl)</td>
<td>Membrane-controlled TTS</td>
<td>Transparent polyester, EVA copolymer</td>
<td>Hydroxyethyl cellulose, ethanol, fentanyl</td>
<td>EVA copolymer</td>
<td>Silicone</td>
<td>Fluorocarbon diacrylate-coated polyester</td>
</tr>
<tr>
<td>Estraderm (17β-estradiol)</td>
<td>Membrane-controlled TTS</td>
<td>Transparent polyester, EVA copolymer</td>
<td>Hydroxyethyl cellulose, ethanol, estradiol</td>
<td>EVA copolymer</td>
<td>PIB, mineral oil</td>
<td>Silicone-coated polyester</td>
</tr>
<tr>
<td>Catapress-TTS (Clonidine)</td>
<td>Membrane-controlled</td>
<td>Tan-colored polyethylene, aluminized polyester, EVA co-polymer,</td>
<td>PIB, mineral oil, colloidal silicon dioxide, clonidine</td>
<td>Microporous polypropylene</td>
<td>PIB, mineral oil</td>
<td>Silicone-coated polyester or fluorocarbon diacrylate-coated polyester</td>
</tr>
</tbody>
</table>

FFS, form-fill seal; EVA, ethylene-vinyl acetate; PIB, polyisobutylene

Currently there are many studies being conducted on transdermal systems with different drug candidates in different stages of development.
1.6 General Methods for the Evaluation of TDDS

1.6.1 In vitro Drug Release Study

The in vitro drug release study is carried out using USP-5 Apparatus. It consists of a paddle, vessel assembly from Apparatus 2 and a stainless steel disk assembly to hold the transdermal system at the bottom of the vessel. USP 6 and 7 apparatus can also be used for in vitro release studies. Other appropriate devices may be used, provided they do not sorb, react with or interfere with the specimen being tested. The temperature is maintained at 32°C ± 0.5°C. A distance of 25 ± 2 mm between the paddle blade and the surface of disk assembly is maintained during the test. The vessel may be covered during the test to minimize evaporation. The disk assembly for holding the transdermal system is designed to minimize any “dead” volume between the disk assembly and the bottom of the vessel. The disk assembly holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade (Figure 1.8a-b). In vitro release conditions are given for the evaluation of marketed formulations are given in the Table 1.5.

![Figure 1.8(a) USP Apparatus 5 (Paddle over disk).](image)
Figure 1.8(b) Disk assembly.

Table 1.5 *In vitro* release methodologies for marketed transdermal systems.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Media</th>
<th>Apparatus and conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>250 ml of H₃PO₄ 1 in 1000 ml</td>
<td>USP VII, 10 rpm, Temp 32 ± 0.3 °C</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>500 ml of sodium acetate buffer pH 4</td>
<td>USP V, 50 rpm, Temp 32 °C</td>
</tr>
<tr>
<td>Ethinyl Estradiol; Norelgestromin</td>
<td>900 ml of 0.1% Hydroxypropyl-beta-cyclodextrin</td>
<td>USP V, 50 rpm, Temp 32 °C</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>900 ml of phosphate buffer pH 6.8</td>
<td>USP V, 50 rpm, Temp 32 ± 0.5 °C</td>
</tr>
<tr>
<td>Epolamine</td>
<td>900 ml of Phosphate Buffer, pH 4.5</td>
<td>USP V, 50 rpm, Temp 32 °C</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>900 ml of water</td>
<td>USP V, 50 rpm, Temp 32 °C</td>
</tr>
<tr>
<td>Estradiol (0.05 mg/24 hr and 0.1 mg/24 hr)</td>
<td>900 ml of water</td>
<td>USP V, 50 rpm, Temp 32 ± 0.5 °C</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>20 ml of distilled water</td>
<td>USP VII, 30-60 rpm, 32°C</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>500 ml of NaCl</td>
<td>USP VI, 50 rpm, 32°C</td>
</tr>
</tbody>
</table>

The pressure-sensitive adhesives are evaluated for general adhesive properties as well as for dermal toxicity and human wear.

### 1.6.2 Adhesive Properties

For evaluation of adhesive properties, adhesive laminates are prepared, consisting of a backing sheet or membrane, an adhesive film and a release liner. For the preparation of test laminate in laboratory transfer coating process is used. Pressure-sensitive adhesive can be evaluated on the basis of their three basic properties: peel adhesion, tack and shear strength.
1.6.2.1 Peel adhesion properties

The force required to remove an adhesive coating from a test substrate is referred to as peel adhesion. Molecular weight of the polymer i.e., tackifiers and polymer composition are the variables that determine the peel adhesion properties.

A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at 180° angle, the force required for tape removed is measured. The force is expressed in ounces (or grams) per inch width of tape, with higher values indicating greater bond strength.

Adhesive failure

The pulled out tape does not leave any residue, desirable for transdermal applications.

Cohesive failure

The tape leaves some residue behind, which often signifies a lack of cohesive strength.

Tack properties

Tack is the ability of a polymer to adhere to a substrate with little contact pressure. It is affected by molecular weight, composition of polymer and tackifying resins. In case of TDDS, which are applied with finger pressure, tack is an important property. There are four generally used tests for tack determination namely thumb, rolling ball, quick-stick (peel-tack), and probe test.

Thumb tack test

It is a qualitative test applied for tack property determination of adhesive. In this test, the thumb is simply pressed on the adhesive and the relative tack property is detected. By experience one can differentiate between relative degree of tack.

Rolling ball tack test

This test measures the softness of a polymer that relates to tack. In this test, a stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward-facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is usually expressed in inch. The less tacky the adhesive, further the ball will travel.
Quick-stick (peel-tack) test
The peel force required to break the bond between adhesive and substrate is measured as tack value, which is expressed in ounces (or grams) per inch width. In this test, the tape is pulled away from the substrate at 90°C at a speed of 12 inches/min. The higher values of force required indicate the higher degree of tack.

Probe tack test
The force required to pull the probe away from the adhesive at fixed rate is recorded as tack (expressed in grams). In this test, probe tack tester is used. The tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive, subsequent removal of the probe mechanically breaks it.

Shear strength properties
Transdermal device with adequate cohesive strength will not slip after application and will leave no residue upon removal. Shear strength is the measurement of the cohesive strength of an adhesive polymer. It can be influenced by molecular weight, degree of cross linking and composition of the polymer as well as the type and amount of tackifier added.

In this particular test, adhesive-coated tape is applied onto a stainless steel plate. A specified weight is hung from the tape. Shear strength is determined by measuring the time it takes to pull the tape off the plate parallel. The longer the time taken for removal, greater is the shear strength.

1.6.3 Ex vivo Evaluation

1.6.3.1 Skin models
During the preclinical development of transdermal devices, it is difficult as well as unethical to test products in humans initially, owing to the potential toxicity of pharmaceutical agents. Therefore, traditional skin models from animals have been used for ex vivo and in vivo studies. Practically, it would be advantageous to use human cadaver skin for permeation studies but, for most investigators, human cadaver skin is not readily available. Also, the skin samples are typically obtained from a variety of anatomical sites and after many different disease states, which might alter the percutaneous permeability of the drug.48,49.
Most transdermal testing is performed using hairless mouse skin. However, other models are sometimes used including rat, guinea pig, rabbit and shed snake skin, artificial composite membranes, and, more recently, living skin equivalents\(^\text{50,51}\). Although there are many similar features between these models and human cadaver skin, no model has yet been tested that fully mimics the results obtained with human cadaver skin.

**Hairless mouse skin**

The permeability of other animal models presents a problem when extrapolating *Ex vivo* data to make dosing predictions. The hairless mouse is used predominantly because it is economical, attainable, easy to house and hairless\(^\text{52}\). However, the permeability and lipid composition of hairless mouse skin are very different to those found in human cadaver skin. Hairless mouse skin tends to be very thin with a small stratum corneum and the permeability of hairless mouse skin may increase 30–40-fold higher than human cadaver skin.

**Pig skin**

Weanling pig skin (i.e. skin from a pig that has recently been weaned) is recognized as the closest alternative to human cadaver skin in its permeability and lipid composition and is reported as skin membrane for *Ex vivo* permeation studies\(^\text{53}\). However, there are some slight structural differences between weanling pig and human skin, including bristles, more subcutaneous fat and less vasculature\(^\text{54,55}\). In addition, the intrinsic permeability, partition coefficient and diffusivity of pig skin are very similar to those of human cadaver skin\(^\text{56}\).

**Living skin equivalents**

Recently, the use of living skin equivalents and epidermal equivalents has become popular for transdermal permeation and *in vitro* toxicity studies. The skin equivalents used for permeation testing are typically epidermal or full-thickness skin\(^\text{57}\). Full-thickness skin equivalents are composed of both dermal and epidermal tissues, with the dermis being constituted from a collagen matrix. The epidermal substitutes are composed mainly of a sheet of normal human keratinocytes that have been cultured at the air–liquid interface to insure proper development and terminal
differentiation. These skin equivalents have many advantages, including the ability to eliminate animal experimentation. Also, they use human skin cells, which provide skin properties similar to those found in native human skin. In this context, it is interesting that all of the lipids found in the native human skin are found in skin equivalents, but in reduced quantities. A commonly used epidermal equivalent for permeability testing is EpiDerm™ (Matech, Boston, MA, USA). This consists of normal, human-derived epidermal keratinocytes that have been cultured to form a multilayered, highly differentiated model of the human epidermis.

Polymeric membranes and other artificial membranes have also been used for transdermal experiments even though these membranes lack the complex histological structures present in the human skin. These membranes showed higher permeation relative to animal and human skin models.

The release and skin permeation kinetics of drug from transdermal therapeutic systems can be evaluated, using a two-compartment diffusion cell assembly, under identical conditions. The diffusion cells of either vertical (Franz) or horizontal (Chein-Keshary). The cells consist of (a) donor and (b) receptor compartments (Figure 1.9 and 1.10). The temperature in the bulk of the solution is maintained by circulating thermostated water through a water jacket that surrounds the receptor compartment. It is carried out by mounting individually the full-thickness of skin, which has been freshly excised. The drug delivery systems are applied with their drug-releasing surface in intimate contact with the stratum corneum surface of the skin. The contents of receptor compartment are stirred using magnetic stirring bar at 600-800 rpm. The skin permeation profile of drug is followed by sampling the receptor solution at predetermined intervals for a duration of up to 24 hr and assaying drug concentrations in the sample by a sensitive analytical method, such as HPLC. The release profile of drug from these transdermal therapeutic systems can also be investigated using the same experimental setup without the skin.
Figure 1.9 Diagrammatic illustration of the Ex vivo skin permeation system using Franz diffusion apparatus is shown with TDD system in intimate contact with the stratum corneum surface (Adopted from Ref 63).

Figure 1.10 Diagrammatic illustration of horizontal - type skin permeation system used for the simultaneous study of the controlled release and the skin permeation of estradiol esters from transdermal bioactivated hormone delivery system. (Adopted from Ref 64).
1.6.3.2 Permeation parameters

The cumulative amount of drug permeated was determined and concentration was corrected for sampling effects according to the following equation\textsuperscript{65}:

\[
C_{n}^{1} = C_{n} \left( \frac{V_{T}}{V_{T} - V_{S}} \right) \left( \frac{C_{n-1}^{1}}{C_{n-1}} \right)
\]

where \(C_{n}^{1}\) is the corrected concentration of the \(n^{th}\) sample, \(C_{n}\) is the measured concentration in the \(n^{th}\) sample, \(C_{n-1}^{1}\) is the corrected concentration in the \((n-1)^{th}\) sample. \(C_{n-1}\) is the measured concentration of drug in \((n-1)^{th}\) sample. \(V_{T}\) is the total volume of the receiver fluid and \(V_{S}\) is the volume of the sample drawn.

The steady state flux (\(J_{ss}\)) is calculated from the slope of the steady state portion of the line in the plot of drug amount permeated Vs time (h). Permeability coefficient (\(K_{p}\)) was calculated by dividing the flux with concentration of the drug in formulation. The lag time was calculated from the intercept on the time axis in the plot of cumulative amount permeated Vs time. The target flux was calculated using the following equation\textsuperscript{66}. The enhancement ratio was calculated as the ratio of flux obtained with and without penetration enhancer (control).

\[
\text{Target flux} = \frac{C_{SS} \times CLt \times BW}{A}
\]

\(C_{SS}\), the concentration at therapeutic level and \(CLt\) the total body clearance, \(BW\) the standard human body weight of 60 kg, \(A\) represents the surface area of the diffusion cell or TTS.

1.6.3.3 Skin irritation and sensitization study\textsuperscript{67}

Recommended designs for skin irritation and skin sensitization studies for the comparative evaluation of transdermal drug products are delineated below.

**Recommendations for a cumulative skin irritation study**

**Study design:** A randomized, controlled, repeat patch test study in humans is used to find out the irritation of test patch. For comparison a reference formulation (innovator patch) may be used. Placebo patches (transdermal patch without active drug substance) and/or high and low irritancy controls (e.g., sodium lauryl sulphate 0.1 % w/v and 0.9 % w/v sodium
chloride) can be included as additional test arms. The study is conducted in 30 subjects for 22 days.

**Patch application:** Each subject applies one of each of the patches to be tested. Test sites should be randomized among subjects. Patches should be applied for 23 hours (± 1 h) daily for 21 days to the same skin site. At each patch removal, the site should be evaluated for reaction and the patch reapplied. Application of a test patch should be discontinued at a site if predefined serious reactions occur at the site of repeated applications. Application at a different site may subsequently be initiated.

**Evaluations:** Scoring of skin reactions and patch adherence should be performed by a trained and blinded observer at each patch removal, using an appropriate scale. Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of irritations.

**Data presentation and analysis:** Individual daily observations should be provided, as well as a tabulation that presents the percentage of subjects with each grade of skin reaction and degree of patch adherence on each study day. The mean cumulative irritation score, the total cumulative irritation score, and the number of days until sufficient irritation occurred to preclude patch application for all the study subjects should be calculated for each test product, and a statistical analysis of the comparative results should be performed.

**Recommendations for a Skin Sensitization Study**  
*(Modified Draize Test)*

**Study design:** A randomized, controlled study on three test products: the test transdermal patch, reference (innovator) patch and the placebo patch (transdermal patch without the active drug substance).

**Patch application:** Test sites should be randomized among subjects. Two hundred subjects are required for the study and the duration is 6 weeks. The study is divided into three sequential periods:

**Induction Phase:** Applications of the test materials should be made to the same skin sites 3 times weekly for 3 weeks, for a total of 9 applications. The patches should remain in place for 48 hours on weekdays and for 72 hours on weekends. Scoring of skin reactions and patch adherence should be performed by a trained and blinded observer at each patch removal, using an appropriate scale. Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features
indicative of irritation. The percent adherence of the transdermal patches should be assessed using a 5-point scale.

**Rest Phase:** The induction phase is followed by a rest phase of 2 weeks, during which no applications are made.

Challenge Phase: The patches should be applied to new skin sites for 48 hours. Evaluation of skin reactions should be made by a trained blinded observer at 30 minutes and at 24, 48 and 72 hours after patch removal.

**Data presentation and analysis:** The individual daily observations should be provided, as well as a tabulation of the percentage of subjects with each grade of skin reaction and degree of patch adherence on each study day. The mean cumulative irritation score and the total cumulative irritation score for all the study subjects should be calculated for each test product, and a statistical analysis of the comparative results should be performed. A narrative description of each reaction in the challenge phase should be provided, together with the opinion of the investigator as to whether such reactions are felt to be indicative of contact sensitization.

**Table 1.6** Dermal response.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of irritation</td>
</tr>
<tr>
<td>1</td>
<td>Minimal erythema, barely perceptible</td>
</tr>
<tr>
<td>2</td>
<td>Definite erythema, readily visible; minimal edema or minimal popular Response</td>
</tr>
<tr>
<td>3</td>
<td>Erythema and papules</td>
</tr>
<tr>
<td>4</td>
<td>Definite edema</td>
</tr>
<tr>
<td>5</td>
<td>Erythema, edema, and papules</td>
</tr>
<tr>
<td>6</td>
<td>Vesicular eruption</td>
</tr>
<tr>
<td>7</td>
<td>Strong reaction spreading beyond test site</td>
</tr>
</tbody>
</table>

**Table 1.7** An estimate of the adherence of the transdermal system.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90% adhered (essentially no lift off of the skin)</td>
</tr>
<tr>
<td>1</td>
<td>75% to &lt; 90% adhered (some edges only lifting off of the skin)</td>
</tr>
<tr>
<td>2</td>
<td>50% to &lt; 75% adhered (less than half of the system lifting off of the skin)</td>
</tr>
<tr>
<td>3</td>
<td>&lt; 50% adhered but not detached (more than half the system lifting off of the skin without falling off)</td>
</tr>
<tr>
<td>4</td>
<td>patch detached (patch completely off the skin)</td>
</tr>
</tbody>
</table>
1.7 Case Study


1.7.1 Development of Carvedilol Transdermal Patches: Evaluation of Physicochemical, Ex vivo and Mechanical Properties

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1.7.1.1 Introduction—selection criteria for drug

Carvedilol is a non-selective β-adrenergic antagonist widely used in the treatment of mild to moderate essential hypertension and stable angina pectoris. It also possesses antioxidant and antiproliferative effects. This may enhance its ability to combat the deleterious effects of sympathetic nervous system activities in heart failure. After a single, 50 mg oral dose of carvedilol, peak plasma concentrations (which vary widely from 20-150 mcg/L) can be achieved within 1-2 h. It was reported to be rapidly absorbed following oral administration, but undergoes extensive first-pass metabolism, leading to a poor bioavailability of 25-35%. In addition to its pharmacokinetic properties, carvedilol has a low dose, low molecular weight (406.5), extensive first-pass effect, lipophilic nature (octanol/water partition coefficient 4.19), and a need for long-term treatment and repetitive dosing, all of which make this drug an interesting candidate for transdermal administration.

1.7.1.2 Materials and Methods

Materials

Carvedilol was a gift sample from Sun Pharma, (Baroda, India). D-limonene was procured from Merk Schuchardt (Hohenbrunn, Germany). Hydroxypropyl methylcellulose E15 (HPMC), hydroxypropyl cellulose (HPC), Eudragit RS 100 (ERS 100), and Eudragit RL 100 (ERL 100) were gift samples from Zydus Cadila (Ahmedabad, India). All other chemicals used were of analytical grade.

Development of Transdermal Systems

Matrix-type transdermal patches containing carvedilol were prepared by solvent evaporation using the film casting technique, employing different ratios of HPMC, HPC, and ERS 100 (or ERL 100) (Table 1.8). The polymers were weighed in requisite ratios by keeping the total polymer weight 3.00 g, allowing for swelling for about 6 h in a solvent mixture (1:1 ratio of dichloromethane, methanol). Dibutyl phthalate was
incorporated as a plasticizer and d-limonene as a penetration enhancer. The drug solution was then added to the polymeric solution, cast onto an anumbra petriplate with a surface area of about 70 sq cm, allowed.

**Table 1.8** Composition, weight and thicknesses of carvedilol Transdermal patches.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug (mg)</th>
<th>Polymers (mg)</th>
<th>Weight* (mg)</th>
<th>Thickness* (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HPMC E 15</td>
<td>ERS 100</td>
<td>HPC</td>
</tr>
<tr>
<td>F1</td>
<td>300</td>
<td>3000</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>F2</td>
<td>300</td>
<td>2400</td>
<td>600</td>
<td>–</td>
</tr>
<tr>
<td>F3</td>
<td>300</td>
<td>2400</td>
<td>–</td>
<td>600</td>
</tr>
<tr>
<td>F4</td>
<td>300</td>
<td>2400</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>F5</td>
<td>300</td>
<td>2400</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>F6</td>
<td>300</td>
<td>2400</td>
<td>–</td>
<td>300</td>
</tr>
<tr>
<td>F7</td>
<td>300</td>
<td>2400</td>
<td>300</td>
<td>–</td>
</tr>
<tr>
<td>F8</td>
<td>300</td>
<td>2400</td>
<td>300</td>
<td>300</td>
</tr>
</tbody>
</table>

Notes: 20% v/w dibutyl phthalate to the total polymer weight, incorporated as plasticizer 8% v/w of d-limonene to the total polymer weight, as penetration enhancer Each patch (3.14 cm$^2$) contains 12.5 mg of carvedilol. *Results are mean ± SD (n=6).

1.8 Evaluation of Transdermal systems

1.8.1 Weight and Thickness Variation Studies

Six films from each series were weighed individually and their average weight was calculated. The thickness of the patch was measured at six different points using digital gauze (Mitatoyo, Japan). For each formulation, six randomly selected patches were used.
1.8.2 Drug Content

Patches from each formulation series (n=3) of 3.14 cm² area were cut into pieces. The pieces were taken in a 100 ml volumetric flask and dissolved in 0.5% w/v sodium lauryl sulphate solution. The solution was filtered through a 0.45 µm membrane filter and drug content was analyzed using a UV/visible spectrophotometer at 244 nm.

1.8.3 Preparation of Rat Abdominal Skin

Albino rats weighing 150-200 g were sacrificed using anaesthetic ether. The hair of test animals was carefully removed with electrical clippers, and the full thickness of the skin was removed from the abdominal region. The epidermis was prepared surgically using a heat separation technique, which involved soaking the entire abdominal skin in water at 60°C for 45 s, followed by careful removal of the epidermis. The epidermis was washed with water and used for Ex vivo permeability studies.

1.8.4 Ex vivo Permeation Studies

A Franz diffusion cell with a surface area of 3.56 cm² was used for Ex vivo permeation studies. The rat abdominal skin was mounted between the compartments of the diffusion cell with the stratum corneum facing the donor compartment. The stratum corneum side of the skin was kept in intimate contact with the release surface of the transdermal drug delivery system (TDDS) under examination. A dialysis membrane (Himedia, Mumbai, India) with a molecular weight cut-off of 5000 was placed over the skin to secure the patch tightly so that it would not become dislodged from the skin. The receiver phase was 12 ml of phosphate buffered saline (PBS) pH 7.4 containing 40% v/v of PEG 400, stirred at 500 rpm on a magnetic stirrer; the whole assembly was kept at 37 ± 0.5°C. The amount of drug permeated was determined by removing 1 ml of sample at appropriate time intervals up to 24 h; the volume was replenished with an equal volume of PBS pH 7.4 containing 40% v/v PEG 400. The drug content in the samples was determined by high-performance liquid chromatography (HPLC). Cumulative amounts of drug permeated in µg/cm² were plotted against time, drug flux (µg/cm²/h) at steady state was calculated by dividing the slope of the linear portion of the curve by the area of the exposed skin surface (3.14 cm²), and the permeability coefficient was deduced by dividing the flux by initial drug
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load as shown in Table 1.9. The target flux was calculated using the following equation

\[ J_{\text{target}} = \frac{C_{\text{SS}} C_{\text{L}T} \text{BW}}{A} \]

A represents the surface area of the transdermal patch (i.e., 3.14 cm\(^2\)), BW the standard human body weight of 60 kg, C\(_{\text{SS}}\) the carvedilol concentration at the therapeutic level and CL\(_{\text{T}}\) the total clearance; the calculated target flux value for carvedilol was 24.94 µg/cm\(^2\)/h.

To predict the release behavior of carvedilol from the TDDS, an in vitro release study was carried out by using a dialysis membrane in place of rat abdominal skin and the drug content in the samples was estimated using HPLC. 

Table 1.9 Assay, in vitro release, Ex vivo skin permeation, transdermal Flux, permeability coefficient and lag time of carvedilol transdermal patches.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Assay(^a) (0/0)</th>
<th>(Q_{12}^{\text{in}}) (mg)</th>
<th>(Q_{24}^{\text{tr}}) Permeation (µg/cm(^2))</th>
<th>(J_{24}^{\text{tr}}) (µg/cm(^2)/h)</th>
<th>(K_{p}^{\text{tr}}) (cm h(^{-1}) x (10^{-5}))</th>
<th>(\text{LT}^{f}) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>100.30 ± 2.44</td>
<td>8.68 ± 0.58</td>
<td>744.53 ± 41.21</td>
<td>8.92 ± 0.52</td>
<td>0.22 ± 0.013</td>
<td>1.49 ± 0.01</td>
</tr>
<tr>
<td>F2</td>
<td>100.80 ± 1.76</td>
<td>9.16 ± 0.59</td>
<td>767.41 ± 88.52</td>
<td>9.27 ± 1.11</td>
<td>0.23 ± 0.028</td>
<td>2.37 ± 0.03</td>
</tr>
<tr>
<td>F3</td>
<td>99.84 ± 0.88</td>
<td>11.70 ± 0.71</td>
<td>1981.72 ± 49.91</td>
<td>20.95 ± 1.06</td>
<td>0.53 ± 0.027</td>
<td>2.01 ± 0.02</td>
</tr>
<tr>
<td>F4</td>
<td>100.72 ± 0.28</td>
<td>10.06 ± 0.51</td>
<td>854.62 ± 57.25</td>
<td>10.43 ± 2.01</td>
<td>0.26 ± 0.050</td>
<td>2.18 ± 0.04</td>
</tr>
<tr>
<td>F5</td>
<td>100.32 ± 1.22</td>
<td>12.31 ± 0.39</td>
<td>2987.87 ± 43.12</td>
<td>32.80 ± 3.23</td>
<td>0.82 ± 0.081</td>
<td>1.33 ± 0.01</td>
</tr>
<tr>
<td>F6</td>
<td>100.08 ± 2.23</td>
<td>10.78 ± 0.65</td>
<td>1367.07 ± 41.92</td>
<td>16.23 ± 1.18</td>
<td>0.41 ± 0.030</td>
<td>1.92 ± 0.26</td>
</tr>
<tr>
<td>F7</td>
<td>99.84 ± 2.64</td>
<td>9.81 ± 0.07</td>
<td>836.55 ± 35.68</td>
<td>10.30 ± 0.28</td>
<td>0.26 ± 0.007</td>
<td>2.37 ± 0.07</td>
</tr>
<tr>
<td>F8</td>
<td>99.52 ± 2.22</td>
<td>10.64 ± 0.17</td>
<td>1286.05 ± 15.31</td>
<td>15.31 ± 0.60</td>
<td>0.38 ± 0.015</td>
<td>1.79 ± 0.07</td>
</tr>
</tbody>
</table>

\(^a\)values represent mean ± SD; \(^b\)Cumulative amount released; \(^c\)Cumulative amount (µg) of drug permeated per cm\(^2\); \(^d\)transdermal flux; \(^e\)Permeability coefficient; \(^f\)Lag time. Values represent mean ± SD (n= 3)
1.8.5 Moisture Absorption Study

The films were weighed accurately and placed in a desiccators containing 100 ml of a saturated solution of aluminium chloride (79.50% relative humidity, RH). After 3 days, the films were taken out and weighed, and the percentage of moisture uptake was calculated as the difference between final and initial weight.

1.8.6 Moisture Content

The patches were weighed and kept in a desiccators containing calcium chloride at 40°C for 24 h. The final weight was noted when there was no further change in the weight of the patch. The percentage of moisture content was calculated as the difference between initial and final weight.

1.8.7 Water Vapor Transmission (WVT) Studies

WVT studies performed using a modification of the method described by Kusum et al. Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1 g of anhydrous calcium chloride was placed; the film was fixed over the brim. The cells were accurately weighed and kept in a closed desiccator containing a saturated solution of potassium chloride to maintain a RH of 84%. The cells were taken out and weighed after 24 h. The amount of water vapour transmitted was found using following formula:

1.8.8 Measurement of Mechanical Properties

The film’s mechanical properties were evaluated using a microprocessor-based advanced force guaze (Ultra Test, Mecmesin, UK) equipped with a 25 kg load cell. Film strips with dimensions 60x10 mm and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the top clamp at a rate of 2 mm/s pulled the strips until the film broke, at which point the force and elongation were measured. The mechanical properties were calculated according to the following formulae. Measurements were run in four replicates for each formulation.
Tensile strength (kg mm\(^{-2}\)) = Force at break (kg)/Initial cross sectional area of the sample (mm\(^2\))

E.B (% mm\(^{-2}\)) = [Increase in length/Original length] x [100/Cross-sectional area]

E.M (kg mm\(^{-2}\)) = [Force at corresponding strain/Cross-sectional area] x [1/Corresponding strain]

Strain = Tensile strength/Elastic modulus

1.8.9 Stability Studies
The stability study was conducted according to ICH guidelines\(^7^8\). Sufficient samples of the formulation F5 were wrapped in aluminium foil and stored in a petri dish at a temperature of 40 ± 2°C and RH of 75 ± 5 % for 6 months. Samples were withdrawn at intervals of 1, 2, 3, and 6 months and analyzed for drug content using the HPLC method.

1.8.10 Drug–Polymer Interaction Study
In order to search for a possible interaction between carvedilol and the polymeric materials of the patches, infrared (IR) spectroscopy and differential scanning calorimetry (DSC) studies were carried out on pure substances and their physical mixtures. The IR spectra were recorded using an IR-Spectrophotometer (PerkinElmer FT-IR, PerkinElmer, Waltham, MA) utilizing the KBr pellet method. DSC studies were conducted using a Differential Scanning Calorimeter (PerkinElmer, Waltham, MA). The samples were scanned at 10°C/min over the temperature range of 30°C-300°C.

1.9 Results and discussion
1.9.1 Weight, Thickness Variation and Drug Content
The weight of the patches ranged from 160.1 ± 3.49 mg for formulation F3 to 160.8 ± 2.50 for F1, and the thickness range was 332.5 ± 16.89 µm for F5 to 363.9 ± 17.91 µm for F1. The results (Table 1.9) showed that the patches were uniform and within the limits, as evidenced by the RSD values, which were less than 6. The drug content ranged from 99.52 ±
2.22% in formulation F8 to 100.8 ± 1.76% in formulation F2. All the formulations were acceptable with regard to carvedilol, as it is evidenced from the RSD values, which were less than 6.

1.9.2 *In vitro* Release Studies

All the transdermal patches were developed and their *in vitro* release profiles analyzed to study the effect of varying polymer concentrations and the effect of a blend of polymers on the kinetics of carvedilol release. Drug release profiles from different formulations are shown in Figure 1.11. Formulation F5 exhibited maximum drug release (12.31 mg) in 24 h, which was significantly (*P* < 0.05) different among all the formulations. The lowest value (8.68 mg) in 24 h was observed in formulation F1, which was composed of HPMC polymer. The increasing order of drug release was F1 < F2 < F7 < F4 < F8 < F6 < F3 < F5. The description of drug release profiles by a model function has been attempted using different kinetics (zero-order, first-order, and the Higuchi square-root model) and using the following equation:

\[ \frac{M_t}{M} = k t^n \]

where \( \frac{M_t}{M} \) is the fraction of drug released at time \( t \), \( k \) is the apparent release rate constant that incorporates the structural and geometric characteristics of the drug delivery system and \( n \) is the diffusional exponent which characterizes the drug’s transport mechanism. The release data was fit into the above model to determine the release mechanism and \( n \) values. The Higuchi square root seemed to be the most appropriate model describing the release kinetics from all of the patches (having a correlation coefficient between 0.952 and 0.998). On the other hand \( n \) values (0.19-0.34) indicated that the amount of drug released was due to Fickian diffusion.
1.9.3 Ex vivo Permeation Studies

The results of in vitro carvedilol permeation through the skin from patches are shown in Table 1.9 and Figure 1.12. The formulation F5 exhibited the maximum (2987.67 µg) cumulative amount of drug permeation in 24 h, which was significantly ($P < 0.05$) different among all the formulations and also different ($P < 0.05$) from the formulation F3, composed of HPMC and HPC as polymers. Formulation F5 showed maximum flux (32.80 µg/cm²/h), which was significantly ($P < 0.05$) different among all the formulations, with a permeation coefficient of $0.82 \times 10^{-2}$ cm/h. When looking at the cumulative amounts of drug permeated through the rat abdominal skin per square centimeter of patch when plotted against time, the permeation profiles of drug seem to follow zero-order kinetics as it is evidenced by correlation coefficients (0.978 to 0.999) better than first order ($r^2$ 0.842 to 0.913) and Higuchi’s equation (Higuchi square-root model; $r^2$ 0.941 to 0.975). When compared to earlier reports, formulation F5 showed 2987.67 µg of drug permeated in 24 h.
with zero-order release kinetics and a flux of 32.8 µg/cm²/h. The formulation composed of HPMC and ERL 100 showed maximum drug release and permeation. In the case of formulation F1, more rigid films were formed that could substantially retard the release of drug from the formulation. The required flux (24.94 µg/cm²/h) was obtained with formulation F5 (32.8 ± 3.23 µg/cm²/h). This indicates that the formulation could release the drug for longer periods with the required flux. The results of drug permeation from Transdermal patches of carvedilol through rat abdominal skin confirmed that carvedilol was released from the formulation and permeated through the rat skin and hence could possibly permeate through human skin.

**Figure 1.12** Permeation of carvedilol from transdermal patches through rat abdominal skin; mean ± SD (n = 3) are presented.

### 1.9.4 Moisture Content and Moisture Absorption Studies

The results of moisture content and moisture absorption studies are shown in Figure 1.13. The moisture content in the patches ranged from
The moisture content in the formulations was found to increase with increases in the hydrophilic nature of the polymers. The rank order of moisture content was F1 > F3 > F6 > F5 > F8 > F4 > F7 > F2. The moisture absorption in the formulations ranged from 8.07 (F2) to 18.78 (F1). Greater moisture absorption was found in formulations F1 and F3; this is because of the polymer’s hydrophilic nature. The order of moisture absorption is F1 > F3 > F5 > F6 > F4 F8 > F7 > F2. The small moisture content in the formulations helps them to remain stable and prevents them from becoming completely dried and brittle films. Again, a low moisture uptake protects the material from microbial contamination and bulkiness\textsuperscript{75,81}.

**Figure 1.13** Moisture absorption and moisture content of carvedilol transdermal patches, mean ± SD (n = 3) are presented: ■ Moisture Absorption, □ Moisture content.
Table 1.10 Tensile strength, elongation at break, elastic modulus, strain, and WVTR of Carvedilol transdermal patches, values represent mean ± SD (n=4).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Tensile Strength (Kg/mm²)</th>
<th>Elongation at Break (% mm²)</th>
<th>Elastic Modulus (Kg/mm²)</th>
<th>Strain</th>
<th>WVTR (g/cm²) x 10⁻³</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>2.35 ± 0.11</td>
<td>8.39 ± 1.15</td>
<td>12.38 ± 0.46</td>
<td>0.19 ± 0.08</td>
<td>4.52 ± 0.003</td>
</tr>
<tr>
<td>F2</td>
<td>0.26 ± 0.16</td>
<td>12.65 ± 0.58</td>
<td>5.13 ± 0.19</td>
<td>0.44 ± 0.03</td>
<td>2.88 ± 0.005</td>
</tr>
<tr>
<td>F3</td>
<td>1.90 ± 0.13</td>
<td>19.17 ± 1.48</td>
<td>9.75 ± 0.36</td>
<td>0.19 ± 0.06</td>
<td>4.51 ± 0.004</td>
</tr>
<tr>
<td>F4</td>
<td>2.07 ± 0.15</td>
<td>13.15 ± 0.80</td>
<td>6.98 ± 0.26</td>
<td>0.30 ± 0.04</td>
<td>3.80 ± 0.007</td>
</tr>
<tr>
<td>F5</td>
<td>2.14 ± 0.20</td>
<td>10.66 ± 3.62</td>
<td>5.89 ± 0.22</td>
<td>0.36 ± 0.04</td>
<td>4.16 ± 0.002</td>
</tr>
<tr>
<td>F6</td>
<td>1.80 ± 0.08</td>
<td>13.35 ± 0.68</td>
<td>7.32 ± 0.27</td>
<td>0.24 ± 0.04</td>
<td>4.29 ± 0.004</td>
</tr>
<tr>
<td>F7</td>
<td>1.50 ± 0.28</td>
<td>11.39 ± 1.14</td>
<td>5.24 ± 0.16</td>
<td>0.29 ± 0.03</td>
<td>3.32 ± 0.005</td>
</tr>
<tr>
<td>F8</td>
<td>1.78 ± 0.22</td>
<td>12.48 ± 1.37</td>
<td>6.01 ± 0.22</td>
<td>0.30 ± 0.04</td>
<td>4.15 ± 0.004</td>
</tr>
</tbody>
</table>

1.9.5 Water Vapor Transmission (WVT) Study

The results of investigation of the patch’s WVT are shown in Table 1.10. The WVT ranged from 2.88 x 10⁻³ to 4.52 x 10⁻³ g/cm². Formulation F1 showed maximum water permeation; this was due to the polymer’s hydrophilic nature, which allowed more WVT through these patches than other patches. Patches that contained HPMC, HPC, and ERL 100 showed more WVT than did ERS 100 patches. As ERS 100 has low permeability in regard to water vapor, patches formulated with ERS 100 as a component showed relatively lower WVT values. The order of WVT was found to be F1>F3>F8>F6>F5>F4>F7>F2.

1.9.6 Mechanical Properties

The tensile testing indicates the film’s strength and elasticity, as reflected by the parameters of tensile strength (TS), elastic modulus (EM), and elongation at break (E/B). A soft and weak polymer is characterized by a low TS, EM, and E/B; a hard and brittle polymer is defined by a moderate TS, high EM and low E/B; a soft and tough polymer is
characterized by a moderate TS, low EM and high E/B; whereas a hard and tough polymer is characterized by a high TS, EM, and E/B. Another parameter strain has been used as an indicator of the film’s overall mechanical quality. A high strain value indicates that the film is strong and elastic. Hence, it is suggested that a suitable Transdermal film should have a relatively high TS, E/B, and strain but a low EM. The results of mechanical properties (TS, E/B, EM and strain) are shown in Table 1.10. Formulation F1 exhibited greater TS and EM values (2.35 kg/mm² and 12.38 kg/mm², respectively) and were significantly (P < 0.05) different among all the formulations. Formulation F5 showed a tensile strength and an elastic modulus of 2.14 kg/mm² and 5.89 kg/mm², respectively. These results revealed that as the concentration of HPMC increased, the TS and EM also increased but E/B values decreased (Figure 1.14). An inverse relation was observed between TS and E/B. These observations indicate that formulation F5 was strong, not brittle, and flexible.

![Figure 1.14 Tensile Strength and Elongation at Break of Carvedilol Transdermal Patches](image)

**Figure 1.14** Tensile Strength and Elongation at Break of Carvedilol Transdermal Patches, ■ Elongation at Break ○ Tensile Strength.
1.9.7 Drug–Polymer Interaction Study

The IR spectral analysis of carvedilol alone showed that the principal peaks were observed at wave numbers of 1630.52, 1590.91, 1500.62, 1455.72, 1255.74 and 956.55. The IR spectra of the physical mixture of carvedilol, HPMC and ERL were 1630.76, 1591.34, 1503.03, 1454.38, 1253.09 and 956.78. However, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers. DSC analysis of pure carvedilol and the physical mixture of carvedilol, HPMC, and ERL 100 showed (Figure 1.15) sharp endothermic peaks at 120°C and 116.7°C respectively. These results revealed a negligible change in the melting point of carvedilol in the presence of polymeric materials, suggesting no interaction between the drug and polymers used in the present study. It is well known that common polymers such as HPMC, ERL and ERS are popular in controlled/sustained release matrix-type patches because of their compatibility with a number of drugs84.

![DSC thermogram](image)

**Figure 1.15** DSC thermograms of carvedilol, HPMC, Eudragit RL 100 and physical mixture of carvedilol and polymers.
1.9.8 Stability Study

The stability of the optimized formulation (F5) was investigated as per ICH guidelines. On storing the TDDS at a temperature of 40 ± 2 °C/75 ± 5% RH for 6 months, 2.31% degradation was observed. As the degradation is less than 5% in the formulation, a shelf life of 2 years could be assigned.

References
4. USP 25. Transdermal delivery from Pharmaceutical dosage forms pp 2223.


71. Monograph of carvedilol from Clarke’s Analysis of Drugs and Poisons, www.medicinescomplete.com


