Chapter - 1

INTRODUCTION
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1. INTRODUCTION

Hypertension is a major disease caused by mental stress and work tension. It is commonly seen in plus forty age group of either sex and a major cause of cardiac arrest and brain hemorrhage. Most of the antihypertensive drugs are available in the form of conventional tablets and capsules. The management of a chronic illness or an acute disease has been accomplished by release of drugs to patients using different conventional dosage forms; like capsules and tablets. This kind of drug delivery system is identified to offer a rapid release of drug. Hence, to attain as well as to uphold the drug concentration within the therapeutically efficient range required for treatment, it is frequently essential to take the conventional form of drug delivery systems numerous times a day. This consequence in a important variation of drug levels in the body. The treatment of hypertension with such conventional dosage form causes fluctuation in drug level hence erratic B.P. and supine hypo-tension is also seen

Further the conventional dosage forms used for the control of infection, fertility and pain may cause adverse effects like vomiting, nausea, toxicity and gastric irritation if they are addicted for long period.\textsuperscript{1}

Continuous I.V. infusion has been recognized as a superior mode of systemic drug delivery that can be modified to maintain a constant and sustained drug levels within therapeutic window for as long as required for effective treatment.
It also provide means of direct entry into the systemic circulation of drugs that are subjected to hepatic first-pass metabolism and/or alleged of generating gastrointestinal incompatibility. Unfortunately, such a type of drug administration involves assured health hazards and thus requires constant hospitalization throughout treatment and needs close medical direction.²

To duplicate the benefits of intravenous drug infusion without its latent hazards, numerous technical developments have been prepared. They have resulted in the development of new techniques for drug delivery. These techniques are capable of controlling rate of drug delivery, sustaining the period of therapeutic activity and/or targeting the delivery of drug to a particular tissue.²

This process has been brought into sharp focus in recent years by the efforts of pharmaceutical films to develop transdermal delivery devices to treat motion sickness, angina, hormone deficiency and hypertension.³

The new drug delivery system has brought regeneration into the pharmaceutical industry for controlled drug delivery. The novel drug delivery systems include transdermal drug delivery system, Ocular drug delivery, nasal drug delivery system etc.

The skin presents a formidable resistance to the absorption, either deliberate or accidental, of chemicals which contact the external surface. Nevertheless, the challenge of transdermal drug delivery has
been accepted by pharmaceutical scientists and, over the last 25 years, considerable progress and achievement have been recorded. Skin is a probable route for systemic drug input and it offers a large surface area (1-2 m$^2$) and very available surface for drug delivery. Transdermal applications, comparative to other routes, are relatively noninvasive, necessitating the easy linkage of a "patch" much like the application of a Band-aid. As a consequence, patient compliance is commonly very excellent - that is, in common, people are fairly comfortable with the use of a simple-looking patch. And also a transdermal system is simply detached either at the end of an application stage, or in the case that sustained delivery is contra-indicated - with the exemption of intravenous infusions, no other release modality offers this benefit.

Even though, transdermal management is partial at present to comparatively few drugs, it has confirmed to be a substantial profitable victory when match up to other "controlled release" technologies. The existing universal market for transdermal systems is about $2 billion yearly. In the US alone, there are more than 30 special products for sale, but only seven vigorous agents (nitroglycerin, Scopolamine, clonidine, fentanyl, estradiol, testosterone and nicotine) have essentially been accepted by the Food and Drug Administration; that is, there are several producers with challenging products that enclose the same drug.
The transdermal route of drug delivery is gaining global acceptance and accolade with the demonstration of percutaneous absorption of a large number of drugs. This kind of drug delivery systems have been developed for controlled drug delivery with the intention of maintaining constant plasma levels, zero order drug input and serves as a constant I.V. infusion. Several transdermal drug delivery systems (TDDS) have recently been developed, aiming to achieve the objective of systemic medication through application to the intact skin.

The concentration of awareness in the potential bio-medical relevance of transdermal controlled drug administration is established in the rising research activities in a number of health care and research institutions in the improvement of different kinds of transdermal therapeutic systems (TTS) for long term uninterrupted infusion of therapeutic agents, comprising antihistamine, anti-anginal, antihypertensive, analgesic and anti-inflammatory drugs.

“Transdermal drug delivery systems are adhesive, drug containing devices of defined surface area that deliver a pre-determined amount of drug to the surface of intact skin at a pre-programmed rate. These systems provide drug systemically at a predictable rate and maintain the rate for extended periods of time.”

4bonding agent, drug having devices of distinct surface area that transport a pre-determined quantity of drug to the surface of intact skin at a pre-programmed speed. These method offer drug
systemically at an expected pace and retain the pace for unlimited periods of time.”

Systemic drug delivery through the skin may have several advantages over conventional drug therapy. It avoids variables that may influence gastro-intestinal absorption, such as the drastic changes in pH along the gastro intestinal tract, food-intake, and intestinal motility. It might avoid systemic first pass metabolism as it circumvents the liver, thereby increasing the bioavailability. Transdermal delivery may produce sustained, constant and controlled levels of drug in the plasma, thereby improving patient compliance since frequent intake of the drug is no longer necessary. The transdermal route can also eliminate pulsed entry into the systemic circulation, which might often cause undesirable side effects. Finally, therapy can easily be terminated by simple removal of the dosage form in problematic cases.

Transdermal therapy, however, also has its disadvantages. The excellent barrier properties of the skin may prevent the entry of drug molecules (wanted and unwanted) from the external environment. Compounds may activate allergic responses and the drug may be metabolized by microflora on the skin’s surface or by enzymes peripheral atmosphere. Compounds may stimulate allergic responses and the drug may be metabolized by enzymes in the skin or by microflora on the skin’s surface. An additional drawback is the inconsistency in skin permeability. So, transdermal therapeutic
methods have been developed to manage the release of the drug and reduce inter-subject distinction\textsuperscript{7,8,14}.

The drug applied topically is circulated, following absorption, first into the systemic circulation and then transported to the tissue, which can be moderately distant from the spot of drug application, to attain its therapeutic action\textsuperscript{15}. 
1.1: The skin site for transdermal drug administration\textsuperscript{20-23}

The skin is one of the most extensive and readily accessible organ with a thickness of of 2.97 ± 0.28mm. It separates the underlying blood circulation network and viable organs from the outside environment. It serves as a barrier against physical and chemical attacks and shields the body from invasion by microorganisms.

Microscopically the skin is a multilayered organ composed of anatomically many histological layers, but it is generally described in terms of three tissue layers; the dermis and epidermis subcutaneous tissue.

1.1.1. Epidermis:

The outermost layer of the skin is composed of stratified squamous epithelial cells. The epithelial cells held together mainly by highly convoluted interlocking bridges, which are responsible for the unique integrity of the skin. The epidermis is thickest in palms, thinner and soles over the ventral surface of the trunk. Microscopically epidermis shows two major parts one is stratum corneum and the other is stratum germinativum.

1.1.2. Dermis:

It is made of a network of robust collagen fibres of fairly uniform thickness with regularly spaced cross striations. This network or gel structure is responsible for the elastic properties of the skin.
Beneath the epidermis, the fibrous tissue opens out and merges with the fat containing subcutaneous tissue.

### 1.1.3. Subcutaneous fat tissue:

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

### 1.2. Permeation pathways

The appendageal route and the epidermal routes to penetrate normal intact human skin. For drugs which primarily cross the integral horny layer, two possible micro routes of entry subsists, the transcellular (or intracellular) and intercellular pathways. The primary pathway taken by a permeant is determined essentially by the partition coefficient ($\log K$). Hydrophilic drugs separation preferentially into the intracellular domains, while lipophilic permeants (octanol/water $\log K > 2$) via the intercellular route pass through the stratum corneum. The majority permeants infuse the stratum corneum by both routes. Yet, the twisted intercellular pathway is broadly considered to offer the primary route and key barrier to the infiltration of most drugs$^{24}$.

### 1.3. Different transdermal drug delivery systems$^{27, 28}$

They can be categorized according to the technical basis of their approach into the subsequent four categories:

- Polymer membrane permeation controlled – TDDS.
- Polymer matrix diffusion controlled – TDDS.
Drug reservoir gradient controlled – TDDS.

Micro reservoir dissolution controlled – TDDS.

1.3.1. Polymer membrane permeation controlled - TDDS.

In this method the drug reservoir is inserted between a rate-controlling polymer membrane and a drug impermeable backing laminate. The drug molecules are allowed to discharge only through the rate-controlling polymeric membrane. In the drug reservoir partition the drug solids are dispersed equivalently in a solid polymer matrix, suspended in an unaffected, sticky liquid medium to form a glue like suspension or suspended in a releasable solvent to form an apparent drug solution. The rate controlling membrane can be either a microporous or a nonporous polymeric membrane e.g., ethylene-vinyl acetate copolymer, with a definite drug permeability. On the exterior surface of the polymeric membrane a thin coating of drug compatible hypoallergenic pressure-sensitive adhesive polymer, e.g., silicone adhesive may be useful to offer close contact of the TDD system with the skin surface.

1.3.2. Polymer matrix diffusion controlled – TDDS.

This drug reservoir having polymer disk is then accumulated into an occlusive base-plate in a partition formulated from a drug impermeable plastic support. As an alternative of covering the adhesive polymer directly on the plane of the medicated disk, in this
method the adhesive polymer is applied along the boundary of the patch to form a strip of adhesive rim adjoining the medicated disks.

Otherwise the polymer matrix dispersing type TDD system can be formulated by directly diffusing the drug in a pressure – sensitive, gum polymer, e.g., polyacrylate, and then covering the drug-dispersed adhesive polymer by solvent casting or hot melt onto a flat sheet of a drug-impermeable backing coat to form a single sheet of drug reservoir.

1.3.3. Drug reservoir gradient – controlled TDDS.

To surmount the non-zero order drug release profiles, polymer matrix drug dispersion type TDD systems can be altered to have the drug loading point assorted in an incremental way, forming a rise of drug reservoir along the diffusional pathway crosswise the multilaminate, adhesive layers. e.g. Deponit®.

1.3.4. Micro reservoir dissolution-controlled TDDS.

This kind of drug delivery system can be measured as a fusion of the reservoir-and matrix dispersion-type drug delivery systems. In this approach the drug reservoir is produced by initially suspending the drug solids in an aqueous solution, of water-miscible drug solublizer, e.g., polyethylene glycol, and then homogenously dispersing the drug suspension, with restricted aqueous solubility in a lipophilic polymer, by high-shear mechanical energy, to outline thousands of unleachable microscopic drug reservoirs. A TDD system
is then formed by rising the medicated disk at the core of an adhesive pad. e.g., Nitrodisc®.

With diffusion controlled devices two primarily dissimilar methodologies can be used; discharge of active agent from monolithic devices and discharge of active agent from reservoir devices.

1.4. **Advantages of transdermal drug delivery systems.**²⁹, ³⁰

- Avoids the hazard and problem of intravenous therapy.
- By-pass the dissimilarity in the absorption of metabolism connected with the oral administration.
- Allow uninterrupted drug administration and the use of drugs with a short biological half-life.
- Increase the bioavailability and efficiency of drugs during the by-pass of hepatic first-pass elimination.
- Treatment can be sustained or terminated according to the need of the physician.
- The majority of the time lower doses are adequate.
- Allow a fast termination of medication, if required, by just eliminating the TDDS from the skin surface.
- Self administration is possible.
- Better patient compliance.
1.5. Selection of drug candidate for transdermal drug delivery.\textsuperscript{31, 32}

Sensible option of drug material is the most chief choice in the flourishing improvement of a transdermal product.

- The efficient concentration (dose) of the drug should be low.
- A drug with short biological half life is a much enhanced candidate for transdermal delivery.
- The drug should have rationally broad therapeutic index so that individual changeability in skin absorption would not create too much trouble for dosage modification.
- The drug should have an widespread pre-systemic metabolism.
- More is the molecular weight less will be the diffusion rate hence low molecular weight drugs are preferable.
- The drug should not be forever bound in the subcutaneous tissues.