ABSTRACT

Background/aims: This review article compiles the works on drug delivery system, typically the transdermal route, right from its traditionally evolved methods to the advanced and upcoming novel methods. As is known, the objective of any drug delivery system is to supply an appropriate proportion of drug to the desired site of action in the body; to accomplish the desired action. This supply has to be sustained for a specific duration of time, depending upon the drug and the ailment. Such systems, even though look simple, as compared to the oral routes, pose abundant challenges. Definition-wise, transdermal drug delivery systems are the topically administered medications in self-contained, discrete dosage forms of patches which when applied to the skin deliver the drug, through the skin portal to systemic circulation at a predetermined and controlled rate over a prolonged period of time in order to increase the therapeutic efficacy and reduced side effect of drug.

Method: This review starts with the historical background of such developed systems. It explains the advantages and disadvantages of older methods: typically the diffusion and absorption routes. The principle transport mechanism across mammalian skin and the factors that affect the permeability of the skin are classified and its correlation with manufactured delivery systems is done. Physicochemical properties of the penetrant molecule, the drug delivery system and the physiological and pathological condition of the skin are discussed in detail. Recent techniques, based on enhancing the transdermal delivery is then introduced and explained in detail. Different components of such patches, their release mechanism are reviewed thoroughly. Vapor patch and micro-reservoir approach is also explained in detail. A new and evolving area of microneedles is introduced with various details of its fabrication procedures and the methodology is elaborated. The stimuli for release, which can also be engineered, falling under different categories such as electrically-based, ultrasound, pressure based, laser based, and so on. An extremely promising novel route, which introduces nanotechnology and nanomaterials to improvise the conventional transdermal drug delivery system, is then elaborated. Results: We have discussed intricate issues such as enhancement (along with control) of drug release involving skin permeability, providing an added driving force for transport into the skin and avoiding injuries to deeper, living tissues.

Conclusions: The article highlights the three generations of transdermal delivery system, which is poised to make significant impact on drug delivery because it concentrates its effects. This targeting enables stronger disruption of the skin barrier, and thereby more effective transdermal delivery, while still protecting deeper tissues. In this way, novel chemical enhancers, electroporation, cavitational ultrasound and more recently microneedles, thermal ablation and microderm-abrasion have been shown to deliver macromolecules, including therapeutic proteins and vaccines, across the skin in human clinical trials. The third generation TDDS, along with the continuous and regular invention of new devices and new drugs that can be administered via this system are hence set to revolutionise the domain of drug delivery in coming times.

KEY WORDS: Transdermal drug delivery, transport mechanism, skin permeability, microneedles.

1. INTRODUCTION

Proper drug selection and an effective drug delivery play pivotal role attaining optimum therapeutic outcomes. The objective of any drug delivery system is to provide an effective therapeutic amount of drug to the desired site of action in the body to accomplish promptly and sustain the desired drug concentration throughout the dose duration. For decades, oral route has been the most common drug delivery form and about 74% of drugs are taken orally but still are found not as effective as anticipated\(^1\). Even though oral administration has notable advantage of easy administration, it also carries significant drawbacks – namely poor bioavailability due to hepatic metabolism (first pass mechanism) and the inclination to yield rapid blood level spikes (both high and low)\(^2\). To overcome these hurdles, there was a burning need for understanding /development of new drug delivery route/ system; which can improve the therapeutic efficacy and safety of drugs by more precise spatial and temporal placement within the body thereby reducing both the size and number of doses and also increasing its effectiveness with optimum dose concentrations. To achieve these goals and improve such characters transdermal drug delivery system was emerged.
Definition:
Transdermal drug delivery system can be defined as the topically administered medications in self-contained, discrete dosage forms of patches which when applied to the skin deliver the drug, through the skin portal to systemic circulation at a predetermined and controlled rate over a prolonged period of time in order to increase the therapeutic efficacy and reduced side effect of drug. TDDS maintains drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration.

Over the past few decades, developing controlled drug delivery has gradually become important in the pharmaceutical industry. Both the pharmacological responses of a drug viz. desired therapeutic effect and the undesired side effect are dependent on the concentration of drug at the site of action, which in turn depends upon the dosage administered and absorbed at that site. The human skin is most readily accessible surface for drug delivery. Every square centimetres of the skin area consists of around 10-70 hair follicles and 200-250 sweat ducts. Thus, potential of using the intact skin as the port of drug administration to the human body has been recognized from the early time in medical history. But skin is a very difficult barrier to the ingress of materials allowing only small measures of a drug to penetrate over a period of time. Transdermal drug delivery (TDD) means the delivery of drugs across the skin and into the systemic circulation taking advantage of the relative accessibility of the skin, is altogether different from topical drug delivery which can only target the local affected areas. The thorough understanding of morphological, biophysical and physicochemical structure and properties of the skin is immensely important in order to deliver therapeutic agents through the human skin for systemic and desired effects. Transdermal delivery provides an important edge over any other forms of injectables and oral routes by increasing patient compliance and avoiding first pass metabolism (FPM) respectively. At one side it provides controlled and sustained administration of drug and at the other side it allows continuous input of drugs with short biological half-life thereby avoiding pulsed entry into systemic circulation, which often causes undesirable side effects. It will be convenient, especially notable in patches which require only once weekly application. With such a simple dosing regimen, the patient compliance and adherence to drug therapy gets aided. Overall with all its beneficiary properties TDDS can be considered as a potential alternative to oral as well as other routes of drug administration.

2. HISTORY OF TDDS/TIMELINE

Even though the term TDDS has been coined recently the knowledge and history of transdermal drug application has been well known since ancient times. Since years, several cultures have been known to use ointments, pastes, plasters and complex inunctions in the treatment of various disease. The mustard plaster may be considered as an example that has been applied for quite a long time as a home remedy for severe chest congestion. Briefly in this process, Powdered mustard seed (Brassica nigra) was mixed with warm water, and the resulting paste was spread on a strip of flannel and was applied to the patient’s chest with a cloth binding wrapped around the body to hold the plaster in place. The moisture and body warmth activated an enzyme (myrosin) in the mustard that hydrolyzed a glycoside (sinigrin), causing the release of the pungent active ingredient allyl isothiocyanate (CH3=CHCNCS). The most remarkable prototype of modern transdermal medication was Stronger Mercurial Ointment, used as a treatment for syphilis. Initially in 1877 Fleischer declared that the skin is totally impermeable. This was a bold and extreme statement which could not hold for a long time. With a huge number of collective studies and after almost 80 years new ideas started to emerge. Investigations were conducted to determine what caused skin to have barrier properties that prevent molecular permeation. In 1924, Rein proposed that a layer of cells joining the stratum corneum (SC) the outermost layer of the skin — to the epidermis posed the major resistance to transdermal transport. Blank modified this hypothesis after removing sequential layers of SC from the surface of skin and showing that the rate of water loss from skin increased dramatically once the SC was removed. In 1957, Monash proved a superficially located barrier in the skin as an obstacle to the penetration. Finally, Scheuplein and colleagues showed that transdermal permeation was limited by the SC by a passive process. Despite the significant barrier properties of skin, Michaels and coworkers measured apparent diffusion coefficients of model drugs in the SC and showed that some drugs had significant penetrability or permeability. These continuous significant establishments were followed by extensive research ultimately proving that the SC was the main barrier to percutaneous absorption and substances/drugs cannot easily penetrate through it due to its nature. These findings opened up an entirely new area where the approach towards considering skin as impermeable membrane for drug delivery was required to be explored further. On the other side, during the early seventies, the newer forms of medication did not match rapid growth of new drugs. From eighties a sort of reverse trend was witnessed where novel drug delivery system got the limelight instead of search for newer drugs in the field of Research and Development. Mammoth price tag, long drawn time and uncertainty about the return had dampened the discovery of newer drugs and thus the concept of repurposing of drugs or finding out newer and convenient drug delivery routes came into picture. Application of the concepts and techniques of controlled release drug administration helped to construct these novel drug delivery systems which not only extended the potent life of existing drug but also minimized the scope and expenditure of testing required for FDA approval. This new approach led to the progress in the field of transdermal patches in the 70’s, which yielded the first patch approved by the US FDA in 1979 called Transderm-SCOP, a three-day patch delivering scopolamine against motion sickness. Al-
most a decade later, nicotine patches became the first transdermal success, raising the profile of transdermal delivery in medicine to a new height and for the public in general. Today, there are wide range of transdermal delivery systems for delivering different drugs such as estradiol, fentanyl, lidocaine and testosterone; combination patches containing more than one drug for contraception and hormone replacement; and iontophoretic and ultrasonic delivery systems for analgesia. Between 1979 and 2002, a new patch was approved on average every 2.2 years. During 2003–2007, that rate for new approved patch was more than tripled every 7.5 months. Considering the economic status worldwide, despite the small number of drugs currently delivered via this route, it is estimated that worldwide market revenues for transdermal products are US$3B, shared between the USA at 56%, Europe at 32% and Japan at 7%. Overall there have been a huge surge in research and development which made it possible to achieve remarkable progress in the formulation and clinical development of transdermal products for cardiovascular disease or neurological problems like Parkinson’s disease, Alzheimer’s disease, depression, anxiety, attention deficit hyperactivity disorder (ADHD) or cancer for example skin cancer or female sexual dysfunction, post-menopausal bone loss, and urinary incontinence. Overall, these transdermal patches are extremely commodious, user-friendly and provides the ease of termination, if need arises (e.g. systemic toxicity) with less pain sensation while administrating drug candidates and with its economic feasibility and with recent ultra-sophisticated high end developments, TDDS seems to hold major potential as an alternative route for drug delivery.

3. ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM

Figure 1: Advantages of TDDS
4. DISADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM: 32-36

![Disadvantages of TDDS](image)

5. ANATOMY OF SKIN

To improvise the current potential of TDDS it is necessary to understand the very basic of skin anatomy.

![Skin Information](image)
Skin is a multi-layered organ composed of many histological layers. The major divisions of the skin, from top to bottom, are the epidermis, the dermis, and the hypodermis.

**Epidermis:** Stratiﬁed, squamous, keratinizing epithelium. Keratinocytes comprise the major cellular component (> 90%) and are responsible for the evolution of barrier function. Keratinocytes change their shape, size, and physical properties when migrating to the skin surface. Other cells present which are present in this layer include Melanocytes, Langerhans cells, and Markel cells, none of which appears to contribute to the physical aspects of the barrier. Microscopically, the epidermis further divided into five anatomical layers with approximately 100-150 micrometres thick, Stratum corneum (SC) forming the outermost layer of the epidermis, exposing to the external environment.

This is the most important layer to transdermal delivery as its composition allows it to keep water within the body and foreign substances out. SC is large, ﬂat, polyhedral, plate-like envelopes filled with keratin that is made up of dead cells that have migrated up from the stratum granulosum. This skin layer is composed mainly of dead cells that lack nuclei. As these dead cells slough off on the surface, air-ﬁlled stratum disjunctum, they are continuously replaced by new cells from the stratum germinativum (basale). The SC consists of 10-15 layers of corneocytes and varies in thickness from approximately 10-15 μm in the dry state to 40 μm when they are hydrated.

**“Brick and mortar” concept:** The SC is also described as a “brick and mortar” structure where the bricks represent the dead, keratinized cells and the mortar represents the intercellular matrix surrounding the cells, composed of long chain ceramides, free fatty acids, triglycerides, cholesterol, cholesterol sulfate, and sterol/wax esters. The intercellular lipid matrix is generated by keratinocytes in the mid to upper part of the stratum granulosum discharging their lamellar contents into the intercellular space. The initial layers of the SC rearrange to form broad intercellular lipid lamellae which then associate into lipid bilayers. As a result of the SC lipid composition, the lipid phase behavior is different from that of other biological membranes. Water is an essential component of the SC, which acts as a plasticizer to prevent cracking of the SC and is also involved in the generation of natural moisturizing factor which helps to maintain suppleness. To understand the physicochemical properties of the diffusing drug and vehicle influence across SC, it is essential to determine the predominant route of drug permeation within the SC. A molecule travelling via the transcellular route partition into and diffuse through the keratinocyte, but in order to move to the next keratinocyte, the molecule must partition into and diffuse through the lipid lamellae between each keratinocyte. The multiple hydrophilic and hydrophobic domains make a structure resembling brick and mortar like structure and the series of partitioning into and diffusing across this structure is unfavourable for most drugs. Therefore, the intercellular route is now considered to be the major pathway for permeation of most drugs across the SC. There are two possible ways that drug molecules can pass through this brick and mortar structure viz. transcellular route, or simply passing through both keratinocytes and lipids in what could be visualized as a straight path to the dermis and the intercellular route where the molecule stays in the lipid bilayer and winds around the keratinocytes on its way to the dermis. Although both paths are possible, the most common route of drug penetration is the intercellular route because most drug molecules are more soluble in the lipid environment of the bilayer than in the protein environment of the keratinocytes.

**Dermis:** Dermis consists of extensive microvasculature network structures like sweat glands, hair follicles, and the smaller blood vessels. Therefore, in order to have drug delivery via the skin, the drug must pass through the epidermis into the dermis where it can be absorbed by capillaries into the circulatory system. Inner and larger (90%) skin layer comprises primarily of connective tissue and provides supports to the epidermis layer of the skin. The boundary between dermis and epidermis layer is called Dermal-Epidermal junction which provides a physical barrier for the large molecules of drug and cells. It incorporates blood and lymphatic vesicles and nerve endings. Dermis can be divided into two anatomical region; papillary dermis and reticular dermis. Papillary is the thinner outermost portion of the dermis. Collagen and elastin fibres are mostly vertically oriented in the papillary region and connected with the dermal-epidermal junction. In reticular dermis, fibres are horizontally oriented.

**Hypodermis**

The hypodermis is the place with larger blood and lymph vessels where fat is stored. It is the adipose tissue layer which is found in between of dermis and aponeurosis and fasciae of the muscles. The subcutaneous adipose tissue is structurally and functionally well

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**Figure 4: Skin Anatomy**

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**References:**
integrated with the dermis through the nerve and vascular networks. This layer is composed of loose connective tissues and its thickness varies according to the surface of body.

6. DRUG DELIVERY ROUTES ACROSS HUMAN SKIN

When a molecule reaches intact skin, it contacts with the cellular debris, normal flora of microorganisms, sebum and other materials. The molecule then can penetrate by three pathways:

- a) Sweat ducts
- b) Hair follicles
- c) Sebaceous glands (collectively called the shunt or appendageal route)

Or, directly across the SC.

Significant research work has been focussed towards attainment of a better understanding of the structure and barrier properties of the SC. The SC consists of 10-15 layers of corneocytes and varies in thickness from approximately 10-15 µm in the dry state to 40 µm when hydrated. The multi-layered “brick and mortar” like structure of keratin-rich corneocytes (bricks) in an intercellular matrix (mortar) composed primarily of long chain ceramides, free fatty acids, triglycerides, cholesterol, cholesterol sulfate and sterol/wax esters as discussed earlier. The corneocytes are not brick shaped but are polygonal, elongated and flat (0.2-1.5 µm thick, 34-46 µm in diameter). The intercellular lipid matrix is generated by keratinocytes in the mid to upper part of the stratum granulosum discharging their lamellar contents into the intercellular space. In the initial layers of the SC this extruded material rearranges to form broad intercellular lipid lamellae, which then associate into lipid bilayers, with the hydrocarbon chains aligned and polar head groups dissolved in an aqueous layer. As a result of the SC lipid composition, the lipid phase behaviour is different from that of other biological membranes. The hydrocarbon chains are arranged into regions of crystalline, lamellar gel and lamellar liquid crystal phases thereby creating various domains within the lipid bilayers. The presence of intrinsic and extrinsic proteins, such as enzymes, may also affect the lamellar structure of the SC. Water is an essential component of the SC, which acts as a plasticizer to prevent cracking of the SC and is also involved in the generation of natural moisturizing factor (NMF), which helps to maintain suppleness. On an average, there are about 20 cell layers in the SC, each of which is perhaps 0.5 µm in thickness. Yet, the architecture of the membrane is such that this very thin structure limits, under normal conditions, the passive loss of water across the entire skin surface to only about 250 mL/day, a volume easily replaced in order to maintain homeostasis. Electron photo-microscopic examination shows that intracellular region in SC is filled with lipid reach amorphous material. During cornification the lipid composition shifts from polar to neutral constituents. In the dry SC intracellular diffusion volume may be as high as 5% and least 1% of the fully hydrated SC. This intra-cellular volume is at least an order magnitude larger than that (approximate 0-2%) estimated for the intra-appendageal pathway, thus, intracellular diffusion could be significant. Both the structured lipid environment between the cells and the hydrated protein, within a corneocytes plays major role in skin permeability, cell membranes are probably of only minor consequences.

a. Intra cellular: between the cells and
b. Trans cellular: across lipid rich region.

The main barriers to absorption are the dead cells of the SC, restricting the inward and outward movement of drug substances and having high electrical resistance. The SC is a heterogeneous tissue, composed of flattened keratinized cells. The outer layers of these cells are less densely packed than those adjacent to the underlying granular layer. Therefore, the epidermal barrier becomes more impermeable in the lower part and this fact has led to suggestion that a separate barrier exists at this level, the so called SC. These horny cells have lost their nuclei and are physiologically rather inactive. Analysis of penetration data, which are evident from controlled stripping experiments and the detailed picture of the SC, gained from electron microscopy support the idea that the barrier to penetration consists of the keratin-phospholipid complex in the dead and relatively dry cells of the entire SC. Thus as molecules move from the environment into the skin, the rate limiting barrier i.e. the tissue that presents the greatest resistance to the movement of molecules, is the SC. Information is limited about the composition of the barrier. The main cellular components are proteins, lipids and water combined into an ordered structure. The composition of the SC is: cell membrane 5% (lipid & non-fibrous protein), cell contents 85% (lipid-20%, a-Protein-50%, β-Protein-20%, and non-fibrous protein-10%), and Intracellular material 10% (lipid and non-fibrous protein).

Surface lipid has been seen to offer little resistance to passage of compounds. Lipid removal studies from the cutaneous surface direct the research that lipid participate in epidermal water function. Barrier function is restored upon extracted lipids returning to the skin. The resistance of the skin to the passage of water from the sum of the tissue resistance can be written as:

\[ RS = R_{SC} + R_{E} + R_{D} \]

SC = Stratum Corneum; E = Epidermis; S = Skin; D = Dermis; R = Resistance
The diffusional resistance of SC to water is approximately 103 times that of either the viable epidermis or superficial region of dermis. For certain material there may be second barrier to absorption at or near the dermo-epidermal junction and not to penetrate into dermis. Because the SC is dead, it is usually assumed that there are no fundamental differences between in vivo and in vitro permeation.

**EPIDERMAL DIFFUSION**

Physical factors affect diffusion through the horny layer in a passive process. A more complicated process is the percutaneous absorption to systemic circulation where first phase is epidermal diffusion and the second phase is clearance from the dermis. Percutaneous absorption depends on effective blood flow, interstitial fluid movements, lymphatic and perhaps other factors such as combination with dermal constituents. A passive diffusion has two main characteristics:

a. A delay period after the drug is placed on the surface, during which the membrane itself becomes charged with the penetrant.

b. A steady penetration after delay period, which lasts as long as the drug remains in the adequate supply on the surface and is removed from the lower surface. This steady rate is proportional to the concentration difference across the membrane. In case of adequately perfused skin, the rate may be considered equal to the concentration applied. The ratio of the steady rate to the concentration applied should be constant (termed as permeability constant). It is a measure of the permeability of the given skin to the drug in the given vehicle.

Once the dosage form is applied topically, the percutaneous absorption or transdermal permeation can be visualized as a composite of a series of steps:

a. Adsorption of a penetrant molecule onto the surface layers of SC.

b. Diffusion through SC and through viable epidermis.

c. Absorption: the uptake of a substance into systemic circulation.

**PERCUTANEOUS ABSORPTION**

It is a step-wise process of penetration of substances into various layers of skin and permeation across the skin into systemic circulation and can be divided into three parts:

a. Penetration: the entry of a substance into a particular layer.

b. Permeation: the penetration from one layer into another, and is different both functionally and structurally from the first layer.

c. Absorption: the uptake of a substance into systemic circulation.

**Fick’s First Law of Diffusion**

Percutaneous absorption of most drugs is a passive-diffusion process that can be described by Fick’s first law of diffusion:

\[ \frac{dQ}{dt} = JT = P.A.\Delta C \]

JT = total flux transported through a unit area of skin per unit time in steady state (µg/hr)

A = area of the skin

P = the effective permeability coefficient

\( \Delta C \) = drug concentration gradient across the skin

For a systemically-active drug to reach a target tissue, it has to possess some physico-chemical properties which facilitate the absorption of the drug through the skin, and also the uptake of the drug by the capillary network in the dermal papillary layer. The rate of permeation, \( \frac{dQ}{dt} \), across various layers of skin tissues can also be expressed as:

\[ \frac{dQ}{dT} = P_s(C_d - C_e) \]

\( C_d \) and \( C_e \) are, respectively, the concentrations of skin penetrate in the donor phase (stratum corneum) and the receptor phase (systemic circulation)

\( P_s \) = the overall permeability coefficient of the skin

Now,

\[ P_s = K_s D_{ss}/H_s \]

Where,

\( K_s \) = Partition coefficient of the penetrant,

\( D_{ss} \) = Apparent diffusivity of penetrant

\( H_s \) = Thickness of skin

Thus, permeability coefficient (\( P_s \)) may be a constant since \( K_s \); \( D_{ss} \) and \( H_s \) terms are constant under the given set of conditions.

A constant rate of drug permeation achieved, if \( C_d \geq C_e \), then the equation may be reduced to

\[ \frac{dQ}{dT} = P_s C_e \]

And the rate of skin permeation (\( \frac{dQ}{dt} \)) becomes a constant, if the \( C_d \) value remains fairly constant throughout the course of skin permeation. To maintain the \( C_d \) at a constant value, it is critical to make the drug to be released at a rate (\( R_s \)) which is always greater than the rate of skin uptake (\( R_e \)), i.e., \( R_s \gg R_e \).

By doing so, the drug concentration on the skin surface (\( C_s \)) is maintained at a level which is always greater than the equilibrium (or saturation) solubility of the drug in the SC (Ces), i.e., Cd > Ces; and a maximum rate of skin permeation (\( \frac{dQ}{dt} \)) m,

Thus:

\[ \frac{dQ}{dt} = P_s C_e \]

Apparently, the magnitude of \( \frac{dQ}{dt} \) m is determined by the skin permeability coefficient (\( P_s \)) of the drug and its equilibrium solubility in the SC (\( C_e \)).

**7. FACTORS AFFECTING TRANSDERMAL PERMEABILITY**

The principle transport mechanism across mammalian skin is by passive diffusion through primarily the trans-epidermal route at steady state or through transappendageal route at initially, non-steady state. The factors that affect the permeability of the skin are classified into following three categories:
A. Physicochemical properties of the penetrant molecule:

a. Partition co-efficient:
Drug possessing both water and lipid solubility are favourably absorbed through the skin. Transdermal permeability co-efficient shows a linear dependence on partition co-efficient. Varying the vehicle may also alter a lipid/water partition co-efficient of a drug molecule. The partition co-efficient of a drug molecule may be altered by chemical modification without affecting the pharmacological activity of the drug.

c. Enhancement of transdermal permeation:
Due to the dead nature of the SC the release of the drug from the dosage form is less. Penetration enhancers thus can cause the physicochemical or physiological changes in SC and increase the penetration of the drug through the skin. Various chemical substances are found to possess such drug penetration enhancing property.

B. Physicochemical properties of the drug delivery system:

a. The affinity of the vehicle for the drug molecules:
It can influence the release of the drug molecule from the carrier. Solubility in the carrier determines the release rate of the drug. The mechanism of drug release depends on whether the drug is dissolved or suspended in the delivery/carrier system and on the interfacial partition co-efficient of the drug from the delivery system to skin tissue.

b. Composition of drug delivery system:
Composition of drug delivery system may affect not only the rate of drug release but also the permeability of the SC by means of hydration.

c. Skin age:
Foetal and infant skin appears to be more permeable than mature adult skin and therefore percutaneous absorption of topical steroids occurs more rapidly in children than in adults whereas, water permeation has shown to be same in adults and in children.

b. Lipid film:
The thin lipid film on skin surface is formed by the excretion of sebaceous glands and cell lipids like sebum and epidermal cell which contain emulsifying agent may provide a protective film to prevent the removal of natural moisturising factor from the skin and help in maintaining the barrier function of the SC.

c. Skin hydration:
Hydration of SC can enhance transdermal permeability. The rate of penetration study of salicylic acid through skin with dry and hydrated corneum showed that when the tissues were hydrated, the rate of penetration of the most water soluble esters increased more than that of the other esters.

d. Skin temperature:
Raising skin temperature results in an increase in the rate of skin permeation. Rise in skin temperature may also increase vasodilation of blood vessels, which are in contact with skin leading to an increase in percutaneous absorption.

e. Cutaneous drug metabolism:
After crossing the SC barrier, some of the drug reaches the general circulation in active form and some of this in inactive form or metabolic form, because of the presence of metabolic enzymes present in the skin layers. It was reported that more than 95% of testosterone absorbed was metabolized as it present through the skin.

f. Species differences:
Mammalian skin from different species display wide differences
in anatomy in such characteristics as the thickness of SC, number of sweat glands and hair follicles per unit surface area.

g. Pathological injury to the skin:
Injuries to the skin can cause the disturbance in the continuity of SC and leads to increase in skin permeability.

8. IDEAL PROPERTIES OF TDDS:
The ideal properties of Transdermal drug delivery system are:

- Optimum partition coefficient
- Shelf life: 2 years
- Low melting point of drug, <200°C
- Patch size <40cm²
- pH of the saturated solution should be between 5-9

![Figure 7: TDDS properties](image)

9. PATIENT COUNSELLING ISSUES:
Patient counselling is one of the vital parameter while developing a drug or a new technique for a novel drug delivery system. The following list includes some general issues on counselling patients using TDDS.

- The target area should be clean, dry and non-hairy. The patch is to be applied with a reasonable and uniform pressure. Oily, inflamed, broken, or calloused skin should not be used. If hair is present at the intended site, it should be carefully cut and not removed with a depilatory agent, since the latter can damage the SC and alter rate and extent of drug permeation.

- Percutaneous absorption may vary depending upon site of application. Thus, the patient should be encouraged to follow the recommended application sites mentioned in the product. Regions of the skin with thick epidermal layers, such as palms and soles, should be avoided. Post-auricular region with richly innervated blood vessels is best suited for small-sized patches. Despite higher drug permeability, the axillary and scalp regions are unsuitable for application of a transdermal patch. Larger patches are suggested to be applied on the forearm, inner thigh, lower back, or chest.

- As drug release rate is not ensured beyond the designated time, the patch should be worn only for the designated period and not any longer. In special TDDS systems (e.g., nitroglycerin patches), it is required to follow a daily ‘on’ (12-14 hours during the day) and ‘off’ (10-12 hours at night) period of application to prevent drug tolerance.

- Application sites should be rotated for repeated use of transdermal patches. The new patch should not be placed over the site of the patch immediately preceding it to minimize skin irritation and sensitization.

- Patches should be stored in original sealed pouches until use. Premature removal of patch or damage in package may lead to drug loss or altered physicochemical properties of one or more components, resulting in a defective product, such as Transderm-Nitro® Patch, Nitro-Dur® Patch, and other similar products containing nitroglycerin, which is highly volatile.

- Handling of the patch during removal from its package and its application is especially important. Care should be taken to avoid touching or damaging the adhesive surface (which may contain drug) after removal of the release liner.

- When applying a patch to the skin, it should be firmly pressed against the skin with the heel of the hand for about 10 seconds to ensure uniform contact and adhesion.

- Cutting of the patch and applying a portion of it should be avoided as it damages the integrity of the system. This is especially so in the case of reservoir systems where cutting the patch can destroy the control membrane and alter drug release kinetics.

- Adherence to the skin is still the most common problem with patch design. Hence, the patch should be applied at a site that is not easily rubbed off by clothing or movement. If a patch dislodges or falls off prematurely, one may attempt to reapply it provided it has not been contaminated or fallen off for too long. Otherwise, a fresh patch should be applied and worn for a full time period from then onwards before further replacement. However, a well-adhered patch can be left on when showering, bathing, or swimming.

- Upon removal, a used patch should be folded into half with the adhesive layers sticking together, so that it cannot be reused. Since the used patch may contain residual drug, it should be disposed of carefully, making sure that children or pets cannot obtain it. Toxic outcomes are likely to occur if a child or pet chews upon a used patch or ingests it.

- If application of the patch to any area of the skin results in skin irritation or inflammation, the patient should contact the physician and seek medical attention as well as re-evaluation of product used.
10. TDDS CLASSIFICATION:

11. RECENT TECHNIQUES FOR ENHANCING TDDS:

A. Structure-based enhancement techniques:

Transdermal Patches
A transdermal patch or skin adhesive patch is a device, loaded with required drug candidate and usually applied on the skin to transport a specific dose of medication across the skin and into the blood circulation\textsuperscript{28, 29}. The adhesive serves two functions: It is glue in nature that keeps the patch adhered to the skin, and it acts as the suspension that holds the drug. The problems associated with this is the concentration of the drug within the adhesive directly affects the “stickiness” of the adhesive so if the large quantities of drug is to be administered, either the size of the patch have to be increased or the patch needs to be reapplied again and again. There have been a huge number of studies carried out to improve the functionality of TDDS patches and to understand the functions of all its components\textsuperscript{49, 50}. 

![Figure 8: TDDS Classification](image-url)
Components of a transdermal patch

While the rate-limiting step in drug delivery can be either the drug release from the delivery system or its absorption into the skin, a well-designed patch system ensures that the former is the rate-limiting step, in order to provide drug uptake at a predetermined rate that is independent of inter-patient skin variability.

Transdermal patch may include the following components:

Liner:
During storage the patch is covered by a protective liner that is removed and discarded before the application of the patch to the skin. Since the liner is in intimate contact with the TDDS, the liner should be chemically inert.

The release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or Teflon. Other materials used for TDDS liners include, polyester foil and metalized laminate that protects the patch during storage. The liner is removed prior to use.

Drug:
Drug solution is in direct contact with release liner.

Permeation enhancers/Membrane:
These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. Penetration enhancers are incorporated into a formulation to improve the diffusivity and solubility of drugs through the skin that would reversibly reduce the barrier resistance of the skin. Thus allows the drug to penetrate to the viable tissues and enter the systemic circulation.

The flux J of drug across the skin can be written as

\[ J = D \frac{dc}{dx} \]

J = The Flux, D = diffusion coefficient, C = Concentration of the diffusing specetes, X = Spatial coordinate

(a) Solvent
These compounds increase penetration possibly by swelling the polar pathway.

*e.g.:* Water alcohols–Methanol & ethanol, Dimethyl acetamide Propane glycol and Glycerol.

(b) Surfactants
The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

i) Anionic surfactant: - Sodium lauryl sulphate Diacetylsulphosuccinate

ii) Nonionic Surfactant:-Pluronic F1, Pluronic F68

iii) Bile Salt: - Sodium taurocholate, Sodium deoxycholate

Desirable properties for penetration enhancers acting within the skin should be non-irritant, non-sensitizing, non-phototoxic, and non-comedogenic: ideally work rapidly, and the activity and duration of effect should be both predictable and reproducible; have no pharmacological activity within the body—*i.e.* should not bind to receptor sites; work unidirectional, *i.e.* should allow therapeutic agents into the body while preventing the loss of endogenous material from the body; shows barrier properties which must return both rapidly and fully when removed from the skin; show compatibility with formulation and system components; be odorless, tasteless, colorless, and cosmetically acceptable; have a desired solubility parameter that approximates that of the skin.

Polymer Matrix/Matrices:
Polymers are employed in skin preparation and it strengthens the foundation of TDDS. Polymer selection and design are of prime importance in this system. It controls the release of the drug from the device.

*e.g.:* Cellulose derivatives, poly vinyl alcohol, Polypropylene Silicon rubber.

The polymer controls the release of the drug from the device.

Properties:
Types of polymer:

- Natural polymers: Cellulose derivative, Gelatin, Waxes, Proteins, Gum, Shellac, Natural rubber, starch, Chitosan.
- Synthetic Elastomers: Hydrid rubber, silicone rubber, Nitrile, Acrylonitrile, Neoprene.
- Synthetic polymers: Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamide, polyurea, epoxy.

Adhesives:53
The adhesion of TDDS is one of the critical factors to the safety, efficacy and quality of the product. Thus adhesives are vital component that plays an intimate contact between the delivery system with the skin. It is related to drug delivery and therapeutic effect. It carries the drug which can either be dispersed or dissolved in the matrix or the compartment containing drug (solution or suspension) is separated from the adhesive layer by a diffusion controlling membrane, the drug permeates through this adhesive membrane to reach the skin. Quality of bond between patch and skin is of high importance as it directly reflects consistency of drug delivered. The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally. It carries the drug which can either be dispersed or dissolved in the matrix or the compartment containing drug (solution or suspension) is separated from the adhesive layer by a diffusion controlling membrane, the drug permeates through this adhesive membrane to reach the skin. Quality of bond between patch and skin is of high importance as it directly reflects consistency of drug delivered. The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally.

Properties:

- Easily removable
- Inexpensive
- Excellent skin contact
- Nonirritant
- No unwashable residue
- Compatibility with the drug

Pressure sensitive adhesives (PSA):54
The fastening of all transdermal devices to the skin can be done by using a PSA, positioned on the face of the device or in the back of the device and extending peripherally.

- The first approach involves the development of new polymers, which include hydrogel hydrophilic polymers, and polyurethanes.
- The second approach is to physically or chemically modify the chemistries of the PSAs in current use (such as PIBs, silicones, and acrylates). Physical modification refers to the formulation of the base adhesives with some unique additives so that, in synergy with the drug and excipients in the system formulation, the result is enhanced drug delivery and improved skin-adhesion properties. Chemical modification involves chemically incorporating or grafting functional monomers to the conventional PSA polymers in order to improve drug delivery rates.

Backings:
Backings are selected for appearance, flexibility and need for occlusion. Examples of backings are polyester film, polyethylene film and polyolefin film, and aluminum vapor coated layer. Other assiduities are the backing additives leaching out and diffusion of drug or the compositions, through the backing. An overemphasis on the chemical resistance often may leads to stiffness and high occlusivity to moisture vapor and air. It causes the TDDS to lift and may possibly irritate the skin during long-term use.

Plasticizers:
Plasticizers have also been used in many formulations ranging from 5 to 20% (w/w, dry basis). Along with the brittleness and ductility of the film, it is also responsible for adhesiveness of the film with other
surfaces or membranes and improvement in strength of film. Some of its examples are glycerol or sorbitol, at 15%, w/w, dry basis, phthalate esters, phosphate, esters, fatty acid esters and glycol derivatives such as PEG 200, and PEG 400. The selection of an appropriate plasticizer and its concentration has a profound influence on the mechanical properties as well as on the permeability of drugs.

**Types of transdermal patches:**

There are four main types of transdermal patches as following

**Single-layer Drug-in-Adhesive:**

In this system the drug is included directly within the skin-contacting adhesive. In this type of patch the adhesive layer is responsible for the releasing of the drug, and serves to adhere various layers together, along with the entire system to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

The intrinsic rate of drug release:

\[
\frac{dQ}{dT} = \frac{C_r}{1/P_m + 1/P_a}
\]

Where,

- \(C_r\) = the drug concentration in the reservoir compartment and \(P_m\) and \(P_a\) are the permeability coefficients of the adhesive layer and the rate controlling membrane,
- \(P_m\) = the sum of permeability coefficients simultaneous penetrations across the pores and the polymeric material.

\[P_m = \frac{K_{m}}{r} \text{ and } P_a = \frac{K_{a}}{m}\]

Where \(K_{m}/r\) and \(K_{a}/m\) are the partition coefficients for the interfacial partitioning of the drug from the reservoir layer to the adhesive layer.
- \(D_m\) and \(D_a\) are the diffusion coefficients in the rate controlling membrane and adhesive layer, respectively;
- \(h_m\) and \(h_a\) are the thicknesses of the rate controlling membrane and adhesive layer, respectively.

**Multi-layer Drug-in-Adhesive:**

The Multi-layer Drug-in-Adhesive is similar to the Single-layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive. The multi-layer system adds another layer of drug-in-adhesive, usually separated by a membrane. This patch also has a temporary liner-layer and a permanent backing.

In this system the drug directly dispersing the drug in the adhesive polymer and then spreading the medicated adhesive on reservoir layer formulate reservoir. On this a layer of non medicated rate controlled adhesive polymer of constant thickness is applied.

Vapour patch:

In this type of patch the role of adhesive layer not only serves to adhere the various layers together but also serves market, commonly used for releasing of essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

Matrix:

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension, which is in direct contact with the release liner. The adhesive layer in this patch surrounds the drug layer partially overlaying it.
feel any pain since nerve fibers are located into deeper region of the skin. Moreover distance to be traveled by drug will decrease. It can be either a solid type or hollow type. Solid type can be of pike shape, or half arrow shape or may be blunted shape. On an average approx. 400 needles (10-2000 micron height & 10-50 micron width, made up of either silicone or metal) are fabricated onto arrays.

Matrix-dispersion system
In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

- More complex, different polymer compositions to provide drug containing matrix and adhesive
- Often no rate controlling membrane
- Matrix may control drug release

The rate of drug release:
\[
\frac{dQ}{dT} = vA\cdot C_{p}\cdot D_{p}/2t
\]
\(A=\) Initial drug loading dose dispersed in the polymer matrix,
\(C_{p}\) & \(D_{p}\) = Solubility and diffusivity of the drug in the polymer respectively.

Microreservoir system
In this type the drug delivery system is a combination of reservoir and matrix-dispersion system. 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 unreachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents.

Microfabricated Microneedles
These are the devices which are having the features of both the hypodermic needle and transdermal patch that can deliver the drug that transports the drug effectively across the membrane. The systems consists of a drug reservoir and some projections (microneedles) extending from the reservoir, these helps in penetrating the SC and epidermis to deliver the drug. It is engineered to create a physical pathway through the upper epidermis to increase the skin permeability. It damages or produces pores only in SC portion so one does not feel any pain since nerve fibers are located into deeper region of the skin. Moreover distance to be traveled by drug will decrease. It can be either a solid type or hollow type. Solid type can be of pike shape, or half arrow shape or may be blunted shape. On an average approx. 400 needles (10-2000 micron height & 10-50 micron width, made up of either silicone or metal) are fabricated onto arrays.

- Poke with patch approach- Involves piercing into the skin followed by application of the drug patch at the site of treatment.
- Coat and poke approach- Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.
- Biodegradable microneedles- Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.
- Hollow microneedles- Involves injecting the drug through the needle with a hollow bore.

Macroflux
These are devices having an area of around 8cm as well as 300 micro projections per cm² with the length of individual micro projection less than 200µm. Three types of Macroflux have been designed. They include, Dry-Coated Macroflux system-this is used for short period delivery that consists microprojection array coated with medicament that adhered to an elastic polymer adhesive backing.

Metered-Dose Transdermal Spray (MDTS)
It is a liquid preparation in the form of solution that are used topically which is made up of a vehicle that is volatile come nonvolatile in nature, which consists the completely dissolved medicament in solution. The use of MDTS reaches the sustained level and better permeation of the drug via skin. The MDTS has the following potential advantages:
- Improves delivery potential without skin irritation due to its non-occlusive nature
- Increased acceptability
- Dose flexibility
- Simple manufacture

B. Electrically-based enhancement techniques
Iontophoresis
The technique involves passing of current of few milli amperes (usually 0.5 mA/cm²) to skin to a limitedarea using the electrode that is in contact with the formulation to be administered. It is facilitated penetration of ions into surface tissues such as skin, oral mucosa and
other epithelia under an externally applied potential difference. There are three possible mechanisms for enhanced penetration through iontophoresis. Electrorepulsion effect drives the solute into the skin and it is main mechanism of enhanced penetration of molecule. Current induced water transport effect (Electro-osmosis or convective transport) (uncharged and larger water soluble molecules). The possibility of increasing the SC permeability in the presence of a flow of an electric current.

Ideal drug candidate for Iontophoresis

- Aqueous Solubility: > 1 mg/ml
- Charge: pKa or pI < 4 (for acids) > 7.4 (for bases)
- Dose Deliverable: 20 – 50 mg/day for MWt < 1000 Da
  2 – 5 mg/day for 1000 Da < MWt < 5000 Da
  < 1 mg/day for MWt > 5000 Da
- pKa – Ionization constant and pl – Isoelectric point

Pilocarpine delivery can be taken as an example to induce sweat in the diagnosis of cystic fibrosis and Iontophoretic delivery of lidocaine is considered to be a nice approach for rapid onset of anesthesia.

Reverse Iontophoresis\textsuperscript{[32, 41]}

Symmetrical nature of iontophoresis (that transports ions across the skin in both directions of the membrane) has led to its application as a noninvasive method of extracting endogenous substances known as reverse iontophoresis (RI). It is considered as potential tool for therapeutic monitoring. Glucowatch biographer\textregistered; once such product approved by FDA in 2001. It is meant for glucose monitoring. RI also suggested for noninvasive monitoring of phenylalanine levels (phenylketonuria).

Ultrasound

The main drug substance is mixed with a coupling agent (usually with cream, gel or ointment) causing ultrasonic energy transfer from the system to the skin. This process ruptures the lipids present in SC, which allows the medicament to permeate via biological barrier.

Photomechanical Waves

Photomechanical waves significantly affects SC to make it highly permeable to drug substance through a possible permeabilisation mechanism by developing of transient channels.

Electroporation

This is an unique method where short and high-voltage electrical pulses are applied to the skin making the drug diffusion improved with the increasing permeability. The electrical pulses form small pores in the SC, through which transportation of drug occurs. For the safe and painless administration, the electrical pulses are introduced by closely spaced electrodes to reserve the electric field within the SC.

Electro-Osmosis

In electro-osmosis a voltage difference is applied to the charge porous membrane resulting in a bulk fluid or volume flow with no concentration gradients. Velocity based enhancement techniques:

- **Needle-Free Injections**
  - i. **Intraject**
  - ii. **Implaject**
  - iii. **Jet Syringe**
  - iv. **Iject**
  - v. **Mini-ject**

- **Powderject Device**

High-speed gas flow is used to propel the solid drug particles across the skin. This device consists of a gas canister that allows helium gas at high pressure to enter a chamber at the end of which a powdered drug containing drug cassette is placed between two polycarbonate membranes. After release, the instantaneous rupturation of both membranes results in the gas to expand quickly which forms a strong motion like a wave that travels down the nozzle thereby propelling the drug molecule at the speed of 600-900 m/s inside the skin.

C. **Other enhancement techniques:**

- **Transfersomes**-

  Transfersomes breaches the skin barrier along the transcutaneous moisture gradient. The carriers creates a drug depot in the systemic circulation having a high drug concentration. Liposomes are microscopic bilayer vesicles, usually made of phospholipids (phosphatidylcholine) and cholesterol, contain both hydrophilic and lipophilic portions and serving as carriers for polar and non-polar drugs. Niosomes are with a similar morphology, but made of nonionic surfactants, typically alkyl polyoxyethylene ethers, mixed with cholesterol. The lipid bilayers destabilizing component of transfersomes makes thisa deformable vesicles for drug delivery.

- **Medicated Tattoos**-

  Med-Tats are a modification of temporary tattoo containing an active drug substance for transdermal delivery.

- **Skin Abrasion**-

  This involves direct removal or disruption of the upper layers of the skin to provide better permeation of topically applied drug substance. In general, one approach is adopted to create micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules. This process is generally known as Microscissuining.

- **Controlled Heat Aided Drug Delivery (CHADD) System**-

  In CHADD System, the transfer of drug substance to the blood circulation takes place by applying heat to the skin that increases the temperature and ultimately leads to increase in microcirculation and permeability of the blood vessel. It consists of small unit for heating
purpose, placed on top of a conventional patch device. An oxidation reaction occurs within the unit which tends to form heat of limited intensity and duration. MicroPor® (Thermal Creation of Micropores) is one such product based on direct heat induced micropore.

**Laser Assisted Delivery (LAD)**
This involves the exposure of the skin to the laser beam that results in the ablation of the SC without damaging the epidermis. Removal of the SC by this technique helps to improve the delivery of lipophilic and hydrophilic drugs.

Two mechanisms possible: Ablative and Laser induced stress waves (photomechanical waves).

- **Ablation**: The high energy of laser is imparted into the skin to form pores that permit the transit of drug through SC.
- **Laser induced stress waves**: There is transient permeabilization effect of macromolecules through SC due to changes in lacunar system

**Route of delivery**: Transappendageal, transcellular and intercellular

- The laser is applied to target that is in contact with a drug solution or to the drug solution itself. The laser energy is strongly absorbed by the target or surface of water and this produces an ultrasonic pressure wave that propagates through the solution to the drug/skin interface. This wave drives the drug through natural physiological skin pore.

**Magnetophoresis**
The effect of magnetic field on diffusion flux of drug substance was found to enhance with increasing applied strength.

**Synergistic effect of enhancers**
Although the various penetration-enhancement methods discussed above have individually been shown to enhance transdermal drug transport, their combinations are often still more effective and multi advantageous. During the past ten years, several studies have supported this hypothesis, specifically addressing combinations of chemicals and iontophoresis; chemicals and electroporation; chemicals and ultrasound; iontophoresis and ultrasound; electroporation and iontophoresis; and electroporation and ultrasound. In addition to increasing transdermal transport in a possibly synergistic manner, a combination of enhancers can also reduce the required ‘dose’ of each enhancer. In this way, combinations of enhancers could increase safety and efficacy. Although combinations offer opportunities, most commercial efforts have emphasized single enhancers, probably due to the complexity of combining multiple technologies. Combining iontophoresis with chemical enhancers, such as ethanol, oleic acid, DMSO, Azone101 and limonene, has been shown to induce synergistic transport enhancement, which is largely attributed to iontophoresis-induced enhancer delivery into the skin. The synergy between ultrasound and chemicals has been demonstrated using a variety of chemicals, including polyethylene glycol (PEG), isopropyl myristate, linoleic acid and surfactants such as sodium lauryl sul-

**12. PREPARATION OF TDDS**

a. **Asymmetric TPX membrane method**: Heat sealable polyester film with a concave of 1cm dia is used as the backing membrane to fabricated patch in this method. Drug sample is dispensed into the concave membrane, covered by a TPX (poly (4-methyl-1-pentene)) asymmetric membrane, and sealed by an adhesive.

b. **Circular Teflon mould method**: Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butyl phthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hrs. And then poured into a circular Teflon mould. The moulds are to be placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored for another 24 hrs. in a desiccator containing silica gel before evaluation to eliminate aging effects. The type films are to be evaluated within one week of their preparation.

c. **Mercury substrate method**: In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 minutes to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation.

d. **IPM membranes method**: In this method required drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solu-
tion is very poor. The formed gel will be incorporated in the IPM membrane.

c. EVAC membrane method: In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

d. Aluminium backed adhesive film method: Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material are added to the drug solution and dissolved. A custom made aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

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Proliposomes Method: Proliposomes are prepared by carrier method using film deposition technique. Drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. Proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottomed flask which is kept at 60–70°C temperature and the flask is rotated at 80–90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20–30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders proliposomes are placed in a desiccator overnight and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.

h. Freefilm method: Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution has to be poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is to be controlled by placing an inverted funnel over the Petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.

13. EVALUATION OF TRANSDERMAL PATCHES: A. Physicochemical Evaluation: i. Thickness: The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film. ii. Uniformity of weight: Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight. iii. Determination of surface pH Specific numbers of patches are kept in contact with distilled water and excess water is drained and pH noted by pH meter. iv. Drug content determination: An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution. v. Content uniformity test: 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test. The samples so obtained are analyzed by HPLC or U.V. spectrophotometer. vi. Moisture content: The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24h. The films are weighed again after a specified interval until they show a constant
weight. The percent moisture content is calculated using following formula. % Moisture content = Initial weight – Final weight X 100

vii. Moisture Uptake:
Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below.
% moisture uptake = (Final weight – Initial weight ) X 100

viii. Flatness:
A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.
% constriction = \[I_1 - I_2\] X 100
\[I_1 = \text{Final length of each strip}\]
\[I_2 = \text{Initial length of each strip}\]

ix. Folding Endurance:
Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value.

x. Shear strength properties:
It is the measurement of the cohesive strength of an adhesive polymer. Adequate cohesive strength property of a device will mean that it will not slip on application and will leave no residue on removal. It is determined by measuring the time it takes to pull on adhesive coated tape off a stainless steel plate when a specified weight is hung from the tape which pulls the tape in a direction parallel to the plate.

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

\[
\text{Tensile strength} = \frac{F}{a.b} (1+L/l) \\
F = \text{force required to break; } a = \text{width of film; } b = \text{thickness of film; } L = \text{length of film; } l = \text{elongation of film at break point.}
\]

xii. Tack properties:
It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer.

xiii. Thumb tack test:
The force required to remove thumb from adhesive is a measure of tack.

xiv. Rolling ball test:
This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.

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

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

xvii. Peel adhesion properties:
Peel adhesion is the force required to remove an adhesive coating from a test substance. It is tested by measuring the force required to pull a single coated tape, applied to a substance at 180° angle. It should not damage the skin and no residue on the skin.

xviii. Polariscope examination:
This test is to be performed to examine the drug crystals from patch by polariscope. A specific surface area of the piece is to be kept on the object slide and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch.

xix. Percentage Elongation break test:
The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula. Elongation percentage = \[\frac{L_1-L_2}{100 L_2}\]. Where, \(L_1\)is the final length of each strip and \(L_2\) is the initial length of each strip.

B. In vitro release studies:

i. The Paddle over Disc:
This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32 ±5°C.
ii. The Cylinder modified USP Basket:
This method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at 32±5°C.

iii. The reciprocating disc:
In this method patches attached to holders are oscillated in small volumes of medium, allowing the apparatus to be useful for systems delivering low concentration of drug. In addition paddle over extraction cell method may be used.

In vitro permeation studies:
The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages. Usually permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as Franz diffusion cell or keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophilic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature (usually 32±5°C for skin) and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectrophotometrically. Then the amount of drug permeated per centimetre square at each time interval is calculated. Design of system, patch size, surface area of skin, thickness of skin and temperature etc. are some variables that may affect the release of drug. So permeation study involves preparation of skin, mounting of skin on permeation cell, setting of experimental conditions like temperature, stirring, sink conditions, withdrawing samples at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectrophotometrically. Then the amount of drug permeated per centimetre square at each time interval is calculated.

iv. Horizontal-type skin permeation system:
This has been widely used for the evaluation of drug permeation across skin. The cell is divided in receptor and donor compartments with a low solution volume (3.5ml) for each compartment and a small membrane area (0.64cm²). They are continuously stirred by matched set of star-head magnets, which are rotated at a speed of 600rpm. The system is controlled by thermostated water through a water jacket surrounding the two compartments.

v. Franz diffusion cell:
The cell is composed of two compartments: donor and receptor. The receptor compartment has a volume of 5-12ml and effective surface area of 1-5 cm². The diffusion buffer is continuously stirred at 600rpm by a magnetic bar. The temperature in the bulk of the solution is maintained by circulating thermostated water through a water jacket that surrounds the receptor compartment.

vi. Flow-through diffusion cell:
Flow through diffusion cells have the advantage that they can be used when the drug has lower solubility in the receptor compartment. This cell can be fully automated and connected directly to HPLC. They have large capacity donor chamber to allow appropriate loading of the applied compound and a low volume (0.3ml) receiving chamber that ensures rapid removal of penetrant at relatively low pumping rates.

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

i. Animal models:
Considerable time and resources are required to carry out human studies, so animal studies are preferred at a small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments helped to a conclusion that hairless animals are preferred over hairy animals. Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in man.

ii. Human models:
The final stage of the development of a TDDS involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials are then conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug. It is first described by Fieldman and Maibach. They include determination of percutaneous absorption by an indirect method of measuring radioactivity in excreta following topical application of the labelled drug. 14C is generally used for radio labelling. Determination of absorption following topical administration requires the investigator to know the amount of radioactivity retained in the
body or excreted by routes. The percentage of dose absorbed transdermally is then calculated as.

\[
\% \text{ Close absorbed} = \frac{\text{Total radioactivity exerted after topical Administration}}{\text{Total radioactivity exerted intervenes was Administration}}
\]

(a) Reservoir technique
It makes use of the relationship between SC reservoir function and \textit{in vivo} percutaneous absorption to predict \textit{in vivo} penetration. This method involves a simple, short exposure of the skin to the compound under study followed by removal of the SC by tape stripping and analysis of the content of the compound in the SC. For this analysis, it is possible to predict the amount of drug that will penetrate over a longer period of time.

(b) Mass balance technique
The application site is covered with an occlusive chamber, the chamber being replaced by a new one after a particular time interval. Radio labelling techniques are used and the faeces and urine of the patients are subjected to analysis.

(c) Cutaneous toxicological evaluation
The major cutaneous toxicological reaction and the method are following

(I) Contact dermatitis
It can be either contact irritant or contact allergic dermatitis.

Contact irritant dermatitis
It results from direct toxic injury to cell membrane, cytoplasm or nuclei. This is generally manifested (to show, clearly especially a feeling) by inflammation and itching and can occurs from the drug, vehicle, and absorption. Contact irritant dermatitis involves use of animals like rabbits and guinea pig. A major part of the screening deals with testing in humans. Two types of protocols are used.

Ten day primary skin irritation test
A panel of ten subjects is applied daily with the test agent for two weeks at the site to be used in clinical situation. Adverse reaction consisting of erythema and scaling are graded daily prior to the reapplication of the agent on a 0 to 3 scale of none, mild, moderate and servers or a 0 to 6 scale to permit more discrimination.

Twenty one day skin irritation test
Same procedure as mentioned above is repeated but there are 25 volunteers and application is on a daily basis for 5 days a week for 21 days. The following test are the never methodologies for assessing cutaneous toxicity and are non-invasive procedure.

(a) Laser Doppler
This test is based upon the principle that as a laser light beam passes through a specimen, it gets scattered when it strike or fall against either static structure or moving object. Light beam scattered in static tissue does not undergo any frequency shift while those encountering moving object does. Doppler effect by illuminating the skin with a monochromatic laser light and electronically process the signal. The frequency mix of the back scattered light collected by a photo editor system at the skin surface, continuously measure the red cell flux.

(b) Evaporative water loss measurement
Contact irritation also disturbs the skin barrier and causes an excessive water loss from the damaged surface than can be measured by means of evaporimetry.

Contact allergic dermatitis
Contact allergic dermatitis involves a fast immunological reaction to an antigen. The antigen is viewed to be a complex formation of an externally applied compound and skin proteins. The reaction can be easily distinguished clinically from contact irritation types of reaction. Two protocols usually are employed-

(I) Low grade dermatitis is included in 25 volunteers by application of 1- 5% Sodium lauryl sulphate to enhance penetration and maximize any allergic potential. In first 5 days in two weeks and closed test is performed.

(II) 75-200 volunteers under occlusive patch test for 5 applications. The test agent is applied in between 24 hr. rest or 48 hr. without rest. After 7-10 days rest period, challenge is done by closed patch testing and results are interpreted. Agent that shows an allergenic potential may still be used by millions of patients with adverse effect.

14. GENERATION OF TDDS:
Overall TDDS can be categorized broadly in three generations of development. The first generation of systems generated many of current patches by thoughtful selection of target drugs that can cross the skin at therapeutic rates with little or no enhancement. The second generation generated improvements for small molecule delivery by increasing skin permeability and driving forces for transdermal transport. The third generation has been aimed at enabling transdermal delivery of small molecule drugs, macromolecules (including proteins and DNA) and virus based/ other vaccines through targeted permeabilization of the skin’s SC.
A. First-generation transdermal delivery systems\textsuperscript{19,78}

The first generation is mainly the TDDS patches that are currently in clinical use. As a result of the ever-growing advances in patch development and overall public acceptance, a recent demand in first-generation transdermal patches was observed. However, this surge gradually lessened as drugs with appropriate properties for such systems could not be engineered. Skin’s outermost layer called SC (10 to 20 µm) poses as the primary barrier to the first-generation approach. Underneath this SC layer is the viable avascular epidermis (50 to 100 µm) and then rich capillary bedded dermis (1–2 mm) for systemic drug absorption just below the dermal–epidermal junction. Currently, there are two types of simple patch design: The original patch design is a liquid reservoir system where the patch consists of a backing material that is both protective and adhesive, a liquid drug reservoir, and a release membrane. Transderm Scop\textsuperscript{®}, Catapress TTS\textsuperscript{®}, Estraderm\textsuperscript{®} and Androderm\textsuperscript{®} use the liquid-reservoir design (Novartis Consumer Health, Inc. 2006)(Boehringer Ingelheim Pharmaceuticals, Inc 2010)(Novartis Pharmaceuticals Corporation 2005). A more recent design is the adhesive matrix system where the adhesive and the drug are combined in the same layer leaving only three layers to the patch: the backing layer, the drug and adhesive layer, and the protective layer that would be removed before applying the patch to the skin. Most currently available patches, except those previously mentioned are the adhesive matrix design.

B. Second-generation transdermal delivery systems

The second generation of TDDS focuses on skin permeability enhancement with a goal to increase the scope of drugs. These systems attempt to augment the delivery of organic molecules through the SC by disrupting its barrier function and/or by providing a potential driving force for the movement of molecules through the epidermis in a reversible disruption machinery avoiding injury to the skin. However, it can be difficult to disrupt the barrier without causing damage or irritation, especially when using chemical enhancers. The 2\textsuperscript{nd} generation enhancement techniques are limited to small, lipophilic molecules and still have little effect on larger or hydrophilic molecules. 2\textsuperscript{nd} generation enhancement methods include chemical penetration enhancers, gentle heating, and iontophoresis.

The ideal enhancer should

(i) Increase skin permeability by reversibly disrupting SC structure,
(ii) Provide an added driving force for transport into the skin and
(iii) Avoid injury to deeper, living tissues.

However, enhancement methods developed in this generation, such as conventional chemical enhancers, iontophoresis and non-cavitational ultrasound, have struggled with the balance between achieving increased delivery across SC, while protecting deeper tissues from damage. As a result, this second generation of delivery systems has advanced clinical practice primarily by improving small molecule delivery for localized, dermatological, cosmetic and some systemic applications, but has made little impact on delivery of macromolecules.

Conventional chemical enhancers

As the focus has been increasing skin permeability, second-generation delivery strategies have turned largely to the development of chemical enhancers. This is a logical extension of the traditional pharmaceutical toolbox as it primarily involves designing new formulations with chemical excipients. Many effective chemical enhancers disrupt the highly ordered bilayer structures of the intracellular lipids found in SC by inserting amphiphilic molecules into these bilayers to disorganize molecular packing or by extracting lipids using solvents and surfactants to create lipid packing defects of nanometer dimensions. Hundreds of different chemical enhancers have been studied, including off-the-shelf compounds and others specifically designed and synthesized for this purpose, such as Azone (1-dodecylazacycloheptan-2-one) and SEPA (2-n-nonyl-1,3dioxolane). One chal-
challenged by the transcellular route of delivery. Small solvent molecules like ethanol and methanol increases the solubility of drug molecules in the lipid bilayer and thereby enhances the intercellular route of drug movement. Molecules whose structures mimic that of phospholipids, those with a small, polar head and a long, hydrocarbon tail, inserts into the lipid bilayer and increase the fluidity within that layer. If the bilayer is more fluid, it becomes easier for drug molecules to move through it, also enhancing intercellular movement. Examples include glycerol monooleate and lauryl lactate which are currently used in Androderm®, as well as Azone TS®, and the two NexACT® enhancers shown. NexACT® enhancers are proprietary chemical compounds that are approved and being investigated in a number of therapies around the world (NexMed USA 2011). For example, NexACT enhancers are included in the following: a topical alprostadil cream (Vitaros®) approved in Canada to treat erectile dysfunction; an alprostadil-based cream (Femprox®) being investigated in the United States and China for female sexual dysfunction; and a terbinfine-based topical product (MycoVa®) that is being developed in Europe for onychomycosis. Azone TS® and SEPA® are also compounds designed specifically as penetration enhancers. Azone TS is currently in Phase III clinical trials of a reformulated triamcinolone acetonide product (Durhalieve®) (Echo Therapeutics 2011). SEPA is currently in Phase II clinical trials of an econazole lacquer also used to treat onychomycosis (EcoNail®). In early trials of EcoNail®, the product was found to produce high econazole concentrations in the nail bed while clinical safety trials show no systemic detection of econazole. SEPA® has also been investigated with alprostadil and sex hormones such as testosterone, estradiol and progesterone.

Non-cavitational ultrasound
Ultrasound was first widely recognized as a skin permeation enhancer when physical therapists discovered that massaging anti-inflammatory agents into the skin using ultrasonic heating probes increased efficacy. Ultrasound is an oscillating pressure wave at a frequency too high for humans to hear. Although some have hypothesized that the pressure gradients and oscillation associated with ultrasound act as a driving force to move drugs into the skin, it appears that the dominant effect is to disrupt SC lipid structure and thereby increase permeability. The effects of non-cavitational ultrasound on skin permeability have generally been limited to enhancing small, lipophilic compounds. Using more aggressive noncavitational ultrasound conditions has been limited by associated tissue heating that is not targeted to the SC and can damage deeper tissue. Under different conditions, ultrasound can also be used to generate cavitation bubble activity, which has different effects and is discussed below.

Heat as a penetration enhancer
Another form of penetration enhancement is the use of heat to increase the permeability of the skin. Unfortunately, the medical community was made aware that heat can increase the absorption of drugs through the skin in 2005 when the FDA began issuing warnings regarding the safe use of fentanyl patches after deaths had been attributed to wearing the patch while sleeping in heated water beds or
using heating pads. One safe use of heat as a penetration enhancer is the Controlled Heat-Assisted Drug Delivery, or CHADD, system. In a CHADD system, a mix of proprietary powders reacts with the air to generate heat that then warms the skin and increases the delivery of the drug. This heat device can be placed on top of an existing patch or other medication or it can be manufactured in combination with a drug of choice. The most well-known of the CHADD systems is the lidocaine/tetracaine patch system which goes by the brand name Synera®. This system is made by ZARS Pharma and is advertised as the “procedural” treatment before a needle stick to reduce the pain of the procedure. The gentle heat is combined with a lidocaine/tetracaine mix that causes effective analgesia within 20 minutes. If a needle-stick procedure can wait 20 minutes, this can be a great way to make a needle stick easier for a child.

**Iontophoresis**

Iontophoresis has been a centre of mainstream study for increasing transdermal delivery for more than a century by typically applying a continuous low-voltage current. While there can be increased skin permeability, iontophoresis mainly provides an electrical driving force for transport across SC. Charged drugs are moved via electrophoresis, while weakly charged and uncharged compounds can be moved by electrosomotic flow of water generated by the preferential movement of mobile cations (e.g., Na+) instead of fixed anions (e.g., keratin) in the SC. Because iontophoresis does not primarily change the skin barrier itself, it is mostly applicable to small molecules that carry a charge and some macromolecules up to a few thousand Daltons. The strongest benefit of iontophoresis is that the rate of drug delivery scales with the electrical current, which can be readily controlled by a microprocessor. In this way, drug delivery can be turned on and off and even modulated over time to enable complex delivery profiles. However, the maximum current—and therefore the maximum delivery rate—is limited by skin irritation and pain caused by the general inability of iontophoresis to localize its effects to the SC. Guided by these strengths and weaknesses, current applications emphasize the ability of iontophoresis to provide control over drug dosing, because it scales with the amount of charge (i.e., the product of current and time) delivered to the skin. Iontophoresis is currently used clinically to rapidly deliver lidocaine for local anesthesia, pilocarpine to induce sweating as part of a cystic fibrosis diagnostic test and tap water to treat hyperhydrosis (i.e., excessive sweating), as well as extract glucose from the skin for glucose monitoring. A recently approved iontophoretic patch enables patients to periodically activate the patch to administer. In contrast to this costly, microprocessor-controlled system, another recently approved iontophoretic patch involves simply connecting the drug reservoir to a constant-voltage, printed battery that can also have some simple control circuitry and delivers drug until the battery runs out. Although the drug delivery rate is not as well controlled using this low-cost alternative, the total amount of drug administered is controlled, because the total amount of charge transferred across the skin is limited by the battery capacity. An additional alternative that seeks to achieve a balance between low cost and microprocessor control of delivery involves a single-use iontophoretic system in clinical trials for delivery of acyclovir to treat herpes labialis. It is the process of using small amounts of electrical current to move drugs across the skin and can also be used to enhance penetration of drug molecules through the SC. In a Galvanic, or Voltaic cell, the cathode is the electrode that attracts positively charged ions from the solution, thus the word “anion” to describe a negatively charged ion such as Cl⁻. If an anode attracts negatively charged particles, then it will repel positively charged ones. In an iontophoretic system the anode will repel positively charged drug molecules. Because most drugs are formulated as a salt, for instance fentanyl hydrochloride, the drug molecule becomes protonated and takes on a positive charge to the negative charge of the chloride anion. This means that the drug will be repelled away from the anode and through the SC toward the dermis.

The advantages of iontophoresis are that the rate of drug delivery is proportional to the electrical current. Since the amount of current in the system can be controlled, the rate of drug delivery can also be controlled and even varied. In a typical patch system, the rate of delivery is proportional to the size of the patch. This dose-to-size relationship can readily be seen in the size of fentanyl patches. A 12 mcg/h patch has a surface area of 5.25 cm² while a 100 mcg/h patch has an area of 42 cm² or 3.5 times as large as the smallest size.

Ionsys® is an iontophoretic fentanyl system that was approved by the FDA in 2006. It was a small, pre-programmed, needle-free, patient-controlled analgesia (PCA) unit that adhered to the patient’s skin like a patch. It was indicated for short-term, acute postoperative pain in hospitalized patients. The patient initiated a dose of fentanyl by double-clicking a red button on the iontophoretic unit. The system was capable of delivering up to six 40mcg doses/hour and up to 3.2mg of fentanyl in 24 hours. Unfortunately, there were problems with the As opposed to the intricate microprocessor systems used in Ionsys®, there are also simpler systems being developed. One such system is a simple circuit that would deliver a fixed amount of drug until the battery runs out. There is less control over the delivery in this system but the total amount of drug delivered is consistent. This type of system has been studied with granisetron for nausea and vomiting of chemotherapy. Another simple system involves administration of a single-dose of 5% acyclovir cream to treat herpes labialis, or cold sores (PR Newswire 2006). In clinical trials, this one-time dose showed a 1.5-day reduction in healing time, which makes this treatment comparable to currently available treatments. However, penciclovir (Denavir®) must be applied every 2 hours while awake for 4 days and n-docosanol (Abreva®) must be applied 5 times daily until the lesion is healed. This iontophoretic acyclovir has been given the brand name SOLOVIR®. Vyteris makes an iontophoretic delivery system that has been given the name SmartPatch® because the system can be programmed to deliver drug through the skin in a
variety of ways. The Smart Patch® can mimic a single IV injection, a rapid onset drug followed by sustained release, a pulsed delivery, or a bolus dose followed by maintenance. The Smart Patch® is also referred to as the “active” patch to contrast the active, iontophoretic delivery of drugs from this system with the passive diffusion found in a 1st generation patch. Iontophoresis begins to bridge the gap between 2nd and 3rd generation TDDS because it can be used to enhance the delivery of small, organic molecules as well as larger, biological molecules.

C. Third-generation transdermal delivery systems

The third generation of transdermal delivery systems is poised to make significant impact on drug delivery because it concentrates its effects to the SC. This targeting enables stronger disruption of the SC barrier, and thereby more effective transdermal delivery, while still protecting deeper tissues. In this way, novel chemical enhancers, electroporation, cavitation ultrasound and more recently microneedles, thermal ablation and microdermabrasion have been shown to deliver macromolecules, including therapeutic proteins and vaccines, across the skin in human clinical trials. 3rd generation TDDS aim to severely disrupt the SC to allow large molecules to pass into the circulation.

Combinations of chemical enhancers

Recent studies have suggested that suitably designed combinations of chemical enhancers can balance trade-offs between enhancement and irritation based on the hypothesis that certain enhancer combinations are especially potent when present at specific, narrow compositions. This approach enables a strategy to target effects that enhance skin permeability in the SC, but avoids irritation in deeper tissues where the formulation composition becomes diluted or otherwise altered. Such a study was carried out by examining close to 500 different pairs of chemical enhancers formulated to have more than 5000 compositions (19). Dramatically increased enhancement with low skin irritation potential was found, for example, for a combination of sodium laureth sulfate (an anionic surfactant) and phenyl piperazine (a compound with aromatic nitrogen) at concentrations of 0.35 and 0.15 wt%, respectively, in a 1:1 mixture of ethanol and phosphate-buffered saline. In vitro screening results were validated with in vivo delivery of a peptide (leuprolide acetate) to hairless rats. These results suggest that combinations of chemical enhancers may succeed for delivery of macromolecules where individual enhancers have generally failed. Work on this approach continues in industry.

Biochemical enhancers

Recently, peptides have been examined as enhancers of skin permeability. In one approach, phage display has been used to screen a library of peptides, which yielded an 11-amino acid synthetic peptide that increased transdermal delivery of insulin in diabetic rats. Additional analysis suggested that a pathway via hair follicles was targeted. It also has been shown that a natural pore-forming peptide, magainin, can be used to increase skin permeability by a mechanism proposed to target bilayer disruption in SC lipids and not in deeper tissue. The magainin was only effective when used in synergistic combination with a surfactant chemical enhancer, which served the dual purpose of increasing skin permeability to the drug as well as increasing penetration of magainin into the SC. Using a produg approach, cyclosporine has been covalently attached to a polyarginine-heptameter cell-penetrating peptide, which led to increased topical absorption that inhibited cutaneous inflammation. In these examples, the highly specific bioactivity enabled by peptide chemistry can enable delivery via targeted routes through the skin.

Thermal ablation

Thermal ablation selectively heats the skin surface to generate micron-scale perforations in the SC. Transiently heating the skin’s surface to hundreds of degrees for microseconds to milliseconds localizes heat transfer to the skin surface without allowing heat to propagate to the viable tissues below. This spares these tissues from damage or pain. Mechanistically, thermal ablation may involve rapidly vaporizing water in the SC, such that the resulting volumetric expansion ablates micron-scale craters in the skin’s surface. More recent studies suggest that temperatures well above the boiling point of water are needed and that other processes, such as tissue combustion, may be at play. Animal studies have demonstrated the ability of thermal ablation to deliver a number of different compounds, such as human growth hormone and interferon a-2b. Skin heating has been achieved using ohmic micro heaters and radio-frequency ablation. The microscopic length scales of localized skin disruption caused by thermal ablation have resulted in the procedure being well tolerated. Thermal ablation heats the skin to 100s of degrees for very short periods of time (micro- to milliseconds) and forms painless, reversible microchannels in the SC without damaging the underlying tissue. The Prelude SkinPrep System®, developed by Echo Therapeutics, is one such TDDS system (Echo Therapeutics 2011). The Prelude SkinPrep System® is easy to use, low cost, handheld, and painless. The system also contains a feedback control used to achieve optimum permeability without damaging underlying tissue. Echo plans to deliver low and high molecular weight drugs with this system and expects the system to be available by the 3rd quarter of 2011 (Pharmacy Choice 2011). Altea Therapeutics also has a thermal ablation product known as the PassPort® (Cress 2007) (Altea Therapeutics 2010). This device deliver up to 10mg of protein and over one hundred milligrams of hydrophilic drug, making this one of the first TDDS that will deliver significant quantities of a hydrophilic drug. The PassPort® system has been shown effective in transdermally delivering small, organic molecules such as hydromorphone, morphine, and fentanyl. As expected, the patch size for the PassPort® fentanyl delivery system is smaller than the size of a traditional fentanyl patch. In studies by Altea, the thermal ablation patch has a surface area of only 1cm² compared to a marketed fentanyl patch with an area of 5cm². The thermal ablation patch achieves higher serum concentrations than the larger, traditional patch (Altea Therapeutics 2010). Perhaps, more interesting than novel ways to deliver small molecules such as fentanyl are novel ways to deliver larger macromolecules such as insulin. Iontophoresis is being investigated as one of these
novel delivery technologies. As opposed to oral dosage forms or patch applications, diabetics must endure needle sticks multiple times a day and there has been no significant advance in the delivery of insulin since its introduction in the 1920s. The PassPort® system has also been shown to be effective in transdermally delivering insulin. Phase I clinical trials show that the PassPort® system was able to deliver a therapeutically significant amount of insulin through the skin. Clinical studies are also underway using the PassPort® system to deliver macromolecules such as interferon-alpha, parathyroid hormone, and hepatitis B surface protein antigen. One way to create these thermal ablation microchannels in the skin is by using radio frequency (RF) waves. These waves cause ions in the surrounding cells to vibrate, the vibrations cause heat, the heat causes evaporation, and the evaporation of water from the cells causes ablation. TransPharma has created the ViaDor® System which uses RF energy to cause thermal ablation of the SC (TransPharma Medical Ltd. 2008). In partnership with Eli Lilly, this TDDS is in clinical trials with a GLP-1 agonist to treat type II diabetes80, calcitonin for musculoskeletal disorders, and teriparatide to treat osteoporosis. The hand-held ViaDor® System is used to cause ablation, the device is removed, and the patch is folded over the newly formed microchannels.

Cavitational ultrasound89,35

In addition to heating, ultrasound is also known to generate cavitation, which is the formation, oscillation and, in some cases, collapse of bubbles in an ultrasonic pressure field. Cavitation is only generated under specific conditions (e.g., low-frequency ultrasound) that differ from those of ultrasonic heating or imaging devices. The opportunity for transdermal drug delivery is that cavitational bubbles concentrate the energy of ultrasound and thereby enable targeted effects at the site of bubble activity. Because bubbles are more difficult to grow and oscillate within densely-packed tissue, cavitation preferentially occurs within the coupling medium (e.g., a hydrogel) between the ultrasound transducer and skin. The expected mechanism of cavitational ultrasound is that bubbles oscillate and collapse at the skin surface, which generates localized shock waves and liquid microjets directed at the SC. This disrupts SC lipid structure and thereby increases skin permeability for up to many hours without damaging deeper tissues. Cavitational ultrasound is not believed to contribute a significant driving force for transport. Already, cavitational ultrasound has been approved for enhanced delivery of lidocaine through the skin and has been studied extensively in animals for delivery of insulin, as well as heparin, tetanus toxoid vaccine and other compounds. Ultrasound can be applied using hand-held devices, as well as low-profile, cymbal transducers that could be integrated into a patch. Ultrasound has also been used to extract interstitial fluid glucose for diabetes monitoring and to increase skin permeability to small molecules, as well as macromolecules up to tens of kilo Daltons. Lasers have similarly been used to increase skin permeability by a related shockwave mechanism. Physical therapists and athletic trainers have used ultrasound for many years to deliver small molecular weight molecules such as dexamethasone, ketoprofen, or lidocaine to their patients. Using ultrasound to deliver drugs across the skin is also referred to as phonophoresis or sonophoresis. This is the same type of ultrasound technology that is used in lithotripsy to break up kidney stones and gallstones. There are two probable mechanisms of action while using ultrasound is used as a TDDS. First, the application of sound waves to the skin causes increased fluidity in the lipid bilayer, increasing the permeability of the skin using the transcellular pathway. This allows increased delivery of small molecules, such as lidocaine, but would not have much effect on larger molecules such as proteins or vaccines. The other mechanism of action takes advantage of cavitation, or the formation of small gas bubbles, those results from ultrasound treatment. When these bubbles aggregate and burst on the surface of the SC, small holes, or pores, are formed in the SC that would allow for the transport of larger molecules. Some of the drugs that have been studied using cavitational ultrasound to enhance delivery include insulin, heparin, and tetanus toxoid vaccine. An early application of this technology was the SonoPrep® Skin Permeation device made by Sontra. This device was given marketing clearance by the FDA in 2004 and was used to deliver lidocaine as a pre-treatment for needle-stick procedures. The device could pre-treat the skin in as little as 15 seconds and would decrease the time to lidocaine effectiveness from one hour down to 5 minutes. One significant disadvantage of ultrasound treatment was the large size of the device needed to deliver the sound waves. Park and colleagues have reported the use of a small, lightweight array of cymbal transducer to deliver insulin transdermally. The data collected in this study show that the blood glucose level of the control group continued to rise throughout the 90-minute experiment while the blood glucose level of the TDDS group fell during the same study period. The study concluded that the use of this cymbal transducer array shows promise in safely lowering blood glucose to normal, human values.

Microneedles as a penetration enhancer61,81

Microneedles are designed to penetrate the SC and deliver drug without reaching the nerves in the underlying tissues. Microneedles can be 200-750 microns in length and are fabricated in groups called arrays that can contain 150-650 microneedles/cm². Some of the materials that have been used to make microneedles include silicon, metal, sugar, and plastics. Microneedles can be hollow and deliver drug through the pores of the needles or they can be coated with active ingredients that deliver the drug as the microneedles dissolve in the skin. Solid microneedle arrays can even be effective in delivering drug simply by creating temporary holes in the SC that remain in effect long enough for an applied drug solution to enter the dermis. A conceptually straightforward way to selectively permeabilize the SC is to pierce it with very short needles. Over the past decade, microneedles have been specifically developed as a means to deliver drugs into the skin in a minimally invasive manner. Solid microneedles have been shown to painlessly pierce the skin to increase skin permeability to a variety of small molecules, proteins and nanoparticles from an extended-release patch82. Alternatively, drug formulations have been coated on or encapsulated within microneedles for rapid or controlled release of peptides and vaccines in the skin. Hollow
Microneedles have been used to deliver insulin and vaccines by infusion. In general, microneedles (i) increase skin permeability by creating micron-scale pathways into the skin, (ii) can actively drive drugs into the skin either as coated or encapsulated cargo introduced during microneedle insertion or via convective flow through hollow microneedles and (iii) target their effects to the SC, although microneedles typically pierce across the epidermis and into the superficial dermis too. Several recent advances in microneedle design and formulation are worthy of note. Original fabrication methods involving clean room-based sculpting of silicon-based structures have moved to low-cost manufacturing methods to make microneedles out of metals and polymers commonly found in FDA-approved devices and parenteral formulations. Microneedles have been dip coated with a variety of compounds, including small molecules, proteins, DNA, and virus particles. Microneedles have also been made of water-soluble polymers that encapsulate various compounds within the needle matrix. These microneedles dissolve in the skin over a timescale of minutes and thereby leave no sharp medical waste after use. Advances have also been made in delivery to humans using microneedles. In a recent study, naltrexone was administered to healthy volunteers whose skin was pre-treated with microneedles. After applying a naltrexone patch, blood levels of naltrexone reached the therapeutic range. Transdermal delivery without microneedle pre-treatment yielded naltrexone levels below detection. Microneedle treatment is reported to be painless by the volunteers and is generally well tolerated. Other unpublished human studies have demonstrated delivery of parathyroid hormone from coated microneedles, which have advanced from animal studies through clinical trials. Vaccine delivery using microneedles has also been a focus for research. Animal studies have demonstrated delivery of live attenuated virus, inactivated virus, protein sub-unit, and DNA vaccines against influenza, hepatitis B, Japanese encephalitis and anthrax using solid and hollow microneedles. Human studies have demonstrated the reliability of hollow microneedles to achieve intradermal injection without special training. Administration of influenza vaccine using these microneedles has recently progressed through completion of clinical trials and filing for registration in Europe. There are several microneedle projects in various stages of clinical trials. In addition, it is clear that the delivery of insulin and vaccines is a very high priority in microneedle research. One available microneedle product seen is the NanoPass MicronJet®. The MicronJet® is a single-use array of Micro Pyramids that can be used to deliver intradermal doses of liquid medications such as vaccines and insulin. The MicronJet fits a standard syringe, thus replacing the hypodermic needle, and has received approval for marketing from the FDA. Microneedles have been proven to be pain-free and they deliver the vaccine intradermally which has been shown to improve vaccine response rates, especially in the elderly, while using lower doses of the vaccine. Intanza® is a seasonal flu vaccine that has been approved in Europe since 2009. Van Damme and colleagues compared Intanza® vaccine to the traditional IM injection plus an adjuvant in elderly patients. While a slightly higher incidence of site reaction was seen with the microneedle product, these reactions were mild and short-lived. It was also found that microneedle delivery had similar tolerability and immunogenicity to the traditional IM vaccine plus adjuvant. Intanza® seasonal flu vaccine is currently in clinical trials in the US sponsored by Sanofi-Pasteur. These microneedles will even be investigated for patient self-administration in the near future. In addition to vaccine delivery, there is also much research devoted to using microneedles to painlessly deliver insulin though the skin. Gupta and colleagues conducted a small, proof-of-concept study delivering insulin via hollow microneedles to two adult subjects with type I diabetes, one female and one male. Both subjects had similar HbA1c levels, comparable weights, BMI, mean insulin usage/day and insulin to carbohydrate ratio. When microneedles were used to deliver insulin, microneedle trials resulted in higher plasma levels of insulin than with catheter delivery. As expected from the plasma insulin levels, microneedles also resulted in lower postprandial plasma glucose levels than the catheter delivery. The study authors believe that, if combined with current microneedle technologies to sample blood glucose levels intradermally, a complete blood glucose monitoring and treatment system could be developed in one unit. Zosano Pharma has developed what they call ZP Patch Technology®. ZP Patch Technology® uses a delivery device to insert an array of drug-coated microneedles into the skin. This system has efficacy and safety comparable to approved injectables, needs only a few minutes of patch wear for drug delivery, and does not require refrigeration for medication stability. Zosano Pharma reports that over 20,000 ZP Patch® systems have been used in Phase III clinical trials that 30 drugs have been tested in pre-clinical trials, and that 450 patients have been tested with 5 peptides and one vaccine. Current PTH therapy requires a daily injection, the injection pen must be refrigerated, and the pen must be discarded after 28 days of use even if medication remains in the pen. ZP PTH® patch is applied for a few minutes once daily, requires no refrigeration, and has a shelf-life of two years. When compared to conventional therapy (teriparatide injection, [Forteo®]), ZP-PTH® has a more rapid onset, a higher Cmax, and a shorter half-life. Microneedle delivery of PTH has been shown to be more effective than placebo and equally effective as conventional therapy at increasing lumbar spine strength. In addition, microneedle delivery of PTH has been shown to be more effective than both placebo and conventional therapy at increasing total hip bone mineral density.

Microdermabrasion has been facilitated by skin abrasion using sandpaper. Initial studies in animals generated strong immune responses to several vaccines when administered topically in combination with a potent adjuvant (i.e.,...
heat-labile enterotoxin of Escherichia coli). More recently, human trials have addressed vaccination against traveller’s diarrhoea and influenza.

**Electroporation**

This method requires the use of short, high-voltage pulses is well known as a method to reversibly disrupt cell membranes for gene transfection and other applications. It has also been shown to disrupt lipid bilayer structures in the skin. Although the electric field applied for milliseconds during electroporation provides an electrophoretic driving force, diffusion through long-lived electropores can persist for up to hours, such that transdermal transport can be increased by orders of magnitude for small model drugs, peptides, vaccines and DNA. Recently, it has been shown to deliver a model peptide vaccine into the skin of mice to generate a strong cytotoxic-T lymphocyte response. Because the SC electrical resistance is orders of magnitude greater than deeper tissues, the electric field applied during electroporation is initially concentrated in the SC. However, upon electroporation of SC lipid bilayers, SC resistance rapidly and dramatically drops, and the electric field correspondingly distributes to a greater extent into the deeper tissues, which contain sensory and motor neurons. The associated pain and muscle stimulation can be avoided by using closely spaced microelectrodes that constrain the electric field within the SC. Although electroporation has been studied extensively in animals, this approach to transdermal delivery has received limited attention in humans thus far due largely to the complexity of device design.

**Comparison of transdermal delivery systems:**

In addition to more than 100 drugs formulated as creams and ointments, there are now 19 drugs or drug combinations administered using FDA-approved transdermal delivery systems. Most of these first-generation delivery systems rely primarily on appropriate drug properties that permit absorption into the skin without significant skin permeation enhancement. However, with constant advancements in the field through second- and third-generation transdermal delivery systems are opening the door to transdermal administration of hydrophilic molecules, macromolecules and vaccines. Most enhancement approaches increase skin permeability without providing an added driving force for transdermal transport. Chemical enhancers are an exception, because they can disrupt SC structure as well as increase drug solubility and thereby increase the drug concentration-gradient driving force. Microneedles are another exception, because they not only pierce the skin, but can carry drug into the skin via coating and encapsulation using solid microneedles or infusion through hollow needles. Although electrical methods of delivery can affect skin permeability as well as provide an electrical driving force, iontophoresis acts primarily to drive drugs into the skin and electroporation acts largely to disrupt SC structure. Because iontophoresis provides a transport driving force, it may be especially useful when coupled with another method that increases skin permeability. Such combined enhancement strategies have received previous attention in the literature. Successful transdermal delivery is based on achieving a suitable balance between effective delivery and safety to the skin. Some of the third-generation systems rely on the hypothesis that relatively large, micron-scale defects in the SC should be well tolerated by patients as long as significant damage is not done to living cells in the viable epidermis and dermis. Reports to date suggest that this hypothesis is reasonable, based on data from a growing collection of clinical trials that have advanced through phase 1 safety trials and into phase 2 and 3 studies of efficacy, especially using microneedles and thermal ablation. This may not be surprising, given that the skin reliably repairs itself without scarring or infection after being routinely subjected to microscopic defects caused by scrapes, scratches, shaving, hypodermic injection, and other minor mechanical trauma. Clinical impact relies not only on a transdermal delivery system that administers drugs in a safe and effective manner, but one that is also low-cost and easy to use, given that most transdermal delivery systems are designed for self-administration at home. The various chemical enhancers can be integrated into small, inexpensive patches that patients find convenient. The various physical enhancers may be more effective to deliver macromolecules and vaccines, but are generally driven by hand-held devices that require electrical power. As a result, most physical enhancers rely on relatively costly, re-usable devices that interface with a disposable drug reservoir component. Microneedles are an exception, because they can deliver macromolecules and vaccines, should be inexpensive to manufacture as single-use patches, and do not require a power supply. However, microneedles are also unique in that they are physically invasive, which raises additional safety and sterility considerations.

Looking to the future, it is likely that first-generation patch technology will continue to be used for delivery of small molecule drugs with the right set of properties, especially those drugs that are currently administered orally and by injection that are coming off patent. Second-generation chemical enhancers should find continued use as formulation excipients in topical dermatological creams and ointments and some systemic patches for small molecule drugs. They will probably have little impact on delivery of hydrophilic drugs and macromolecules, because the most effective chemical enhancers generally diffuse out of the SC and irritate deeper tissue. Targeted, third-generation combinations of chemical enhancers and biochemical approaches offer strategies for more targeted enhancement, but are still in early stages of development. Second-generation physical enhancement using iontophoresis has already made clinical impact, especially for rapid, localized delivery to the skin. Its electronic control over delivery rates gives iontophoresis a special property that can be exploited for patient-controlled dosing and other complex delivery profiles. However, because iontophoresis does not substantially change the skin barrier, it appears unlikely to impact macromolecule or vaccine delivery, unless used in combination with other methods that increase skin permeability. Likewise, noncavitational ultrasound has found use for transdermal delivery of anti-inflammatories in the context of physical therapy, but does not appear suitable for delivery of large compounds. Third-generation physical enhancement using cavitational ultrasound and electroporation enhance transdermal de-
livery by disrupting SC on the nanometer scale. Cavitation ultrasound has already been approved for transdermal delivery of lidocaine and may be approved in the future for peptides and other small macromolecules. Although effective, applications of cavitation ultrasound may be limited by the need for a sophisticated device that only increases skin permeability at the nanometer scale and thereby may not be broadly applicable to macromolecules and vaccines. Skin can be disrupted on the micron scale by third-generation physical enhancement using microneedles, thermal ablation and microdermabrasion. These methods have special promise, because they appear broadly capable of delivering not only small molecules, but macromolecules and vaccines as well. A microneedle product for vaccine delivery has been submitted in Europe for regulatory approval and other microneedle and thermal ablation products are proceeding through advanced clinical trials. A limitation of diffusing large compounds through micron-scale disruptions is that diffusivity is a strong inverse function of molecular size. Thus, even though, for example, an inactivated virus particle vaccine can easily fit through a micron-sized hole, it may take a long time to diffuse through. When rapid delivery is desirable, it may be preferable to use microneedles that actively drive macromolecules and drugs into the skin or to combine micron-scale disruption with an added driving force, such as iontophoresis. Overall, transdermal drug delivery offers compelling opportunities to address the low bioavailability of many oral drugs; the pain and inconvenience of injections; and the limited controlled release options of both. Building off the successes of first-generation transdermal patches, second-generation chemical enhancers and iontophoresis are expanding delivery capabilities for small molecules, whereas third-generation physical enhancers (including ultrasound, thermal ablation and microneedles) could enable transdermal delivery of macromolecules and vaccines. These scientific and technological advances that enable targeted disruption of SC while protecting deeper tissues have brought the field to a new level of capabilities that position transdermal drug delivery for increasingly widespread impact on medicine.

15. CONCLUSION:
Transdermal drug delivery offers compelling opportunities to address the low bioavailability of many oral drugs; the pain and inconvenience of injections; and the limited controlled release options of both. Building off the successes of first-generation transdermal patches, second-generation chemical enhancers and iontophoresis are expanding delivery capabilities for small molecules, whereas third-generation physical enhancers (including ultrasound, thermal ablation and microneedles) could enable transdermal delivery of macromolecules and vaccines. All these scientific and technological advances that enable targeted disruption of stratum corneum while protecting deeper tissues have brought the field to a new level of capabilities that position transdermal drug delivery for increasingly widespread impact on medicine. A huge number of research works has been done related to TDDS. Recently new researches have been initiated to introduce newer drugs via this system through various modifications in delivery module as well as modifying the drug and reservoir chemistry. Various devices used to increase the absorption rate and penetration of the drug is also being studied. However, due to certain disadvantages like large drug molecules cannot be delivered, large dose cannot be given, the rate of absorption of the drug is less, skin irritation; etc., the use of TDDS has been limited. But with continuous regular invention of new devices and new drugs that can be administered via this system, the use of TDDS is increasing rapidly in the present time.

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