Transdermal drug delivery system: A mini review

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Abstract
In the last two decades, the transdermal drug delivery has become a proven technology that offers wide range of advantages than conventional route. Because transdermal drug delivery offers controlled as well as predetermined rate of release of the drug into the patient, and it can easily terminate the drug action, whenever is required. First-generation transdermal delivery has delivered small, lipophilic, low dose drugs. Second-generation transdermal delivery has used ultrasound, iontophoresis and chemical enhancers in delivering the drug. Third-generation transdermal delivery has used microneedles, electroporation, thermal ablation, microdermabrasion, in delivering the drug. This review emphasizes the various modules used in delivery of drug with topical application. The main aim of transdermal drug delivery system is to deliver the drug into systemic circulation with minimal inter and intrasubject variability.

Keywords: Transdermal delivery, skin, permeation enhancers, evaluation studies

Introduction
Transdermal Drug Delivery Systems
Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver the drugs for systemic effects at a predetermined and controlled rate. As it is one of the most promising methods for drug application. Transdermal delivery of drugs through the skin to the systemic circulation provides a suitable route of administration for a variety of clinical indications. Transdermal drug delivery device may be active or passive design for the delivery of pharmaceuticals through skin barrier here the drug enters the systemic circulation through diffusion across the skin barrier directly since there is high concentration of drug in the patch and low concentration in the blood the release occurs for prolonged time [2].

Transdermal patch uses a special membrane to control the rate at which the liquid drug enclosed in the reservoir within the patch can pass through the skin and into the bloodstream. Some drugs must be combined with substances, such as alcohol, that increase their ability to pierce the skin in order to be used in a skin patch. Drugs administered through skin patches include scopolamine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to prevent osteoporosis after menopause), nitro-glycerine (for angina), and lidocaine to relieve the pain of shingles (herpes zoster).

Transdermal patches were developed in the 1970s and the first was approved by the FDA in 1979 for the treatment of motion sickness. It was a three-day patch that delivered scopolamine. In 1981, patches for nitro-glycerine were approved, and today there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitro-glycerine, oestradiol, oxybutinin, scopolamine, and testosterone. There are also combination patches for contraception, as well as hormone replacement. Depending on the drug, the patches generally last from one to seven days. The major advantages provided by transdermal drug delivery include the following: improved bioavailability, more uniform plasma levels, longer duration of action subsequent reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval, compared to a decline in plasma levels with conventional oral dosage forms. Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug-degradation effects. Patches can also reduce side effects; for example, oestradiol patches are used by more than a million patients annually. Aroma patches, weight loss patches, and no medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists patches that measure sunlight exposure).
Advantages of transdermal patches [5],
- Topical patches are a painless, non-invasive way to deliver substances directly into the blood.
- Topical patches can bypass first-pass hepatic metabolism
- Termination of medicament can be possible by removing the patch from skin.
- Drug which is, stomach irritant can modify to topical delivery.
- Topical patches have fewer side effects than oral medications.
- Topical patches are easier to use and remember.
- Topical patches are cost-effective.
- Topical patch can release the drug at steady state over the long period of time.
- Topical patch can bypass the enzymes action on it.

Limitation [5],
- TDDS cannot deliver ionic drugs.
- TDDS cannot achieve high drug levels in blood/plasma.
- It cannot develop for drugs of large molecular size.
- TDDS cannot deliver drugs in a pulsatile fashion.
- TDDS cannot develop if drug or formulation causes irritation to skin.
- Limitation of TDDS can be overcome to some extent by novel approaches such as Iontophoresis, electroporation and ultrasound.
- Adjustment of dose is required in order to achieve therapeutic concentration.

Adverse events
In 2005, the FDA announced that they were investigating reports of death and other serious adverse events related to narcotic overdose in patients using Duragesic, the fentanyl transdermal patch for pain control. The Duragesic product label was subsequently updated to add safety information in June 2005. In 2008, two manufacturers of the Fentanyl patch, Alza Pharmaceuticals (a division of major medical manufacturer Johnson & Johnson) and Sandoz, subsequently issued a recall of their versions of the patch due to a manufacturing defect that allowed the gel containing the medication to leak out of its pouch too quickly, which could result in overdose and death. As of 2010, Sandoz no longer uses gel in its transdermal fentanyl patch; instead, Sandoz-branded fentanyl patches use a matrix/adhesive suspension (where the medication is blended with the adhesive instead of held in a separate pouch with a porous membrane) [9].

Anatomy of the Skin [12],
Skin anatomy
The epidermis is the outer layer, serving as the physical and chemical barrier between the interior body and exterior environment; the dermis is the deeper layer providing the structural support of the skin, below which is a loose connective tissue layer, the hypodermis which is an important depot of fat.

Epidermis
The epidermis is stratified squamous epithelium. The main cells of the epidermis are the keratinocytes, which synthesis the protein keratin. Protein bridges called desmosomes connect the keratinocytes, which are in a constant state of transition from the deeper layers to the superficial. The four separate layers of the epidermis are formed by the differing stages of keratin maturation. The epidermis varies in thickness from 0.05 mm on the eyelids to 0.8±1.5 mm on the soles of the feet and palms of the hand. Moving from the lower layers upwards to the surface, the four layers of the epidermis are:
1) Stratum basale (basal or germinativum cell layer)
2) Stratum spinosum (spinous or prickle cell layer)
3) Stratum granulosum (granular cell layer)
4) Stratum corneum (horny layer).
In addition, the stratum lucidum is a thin layer of translucent cells seen in thick epidermis. It represents a transition from the stratum granulosum and stratum corneum and is not usually seen in thin epidermis. Together, the stratum spinosum and stratum granulosum are sometimes referred to as the Malpighian layer.

Stratum Basale
The innermost layer of the epidermis which lies adjacent to the dermis comprises mainly dividing and non-dividing keratinocytes, which are attached to the basement membrane by hemi desmosomes. As keratinocytes divide and differentiate, they move from this deeper layer to the surface. Making up a small proportion of the basal cell population is the pigment (melanin) producing melanocytes. These cells are characterized by dendritic processes, which stretch between relatively large numbers of neighboring keratinocytes. Melanin accumulates in melanosomes that are transferred to the adjacent keratinocytes where they remain as granules. Melanin pigment provides protection against ultraviolet radiation; chronic exposure to light increases the ratio of melanocytes to keratinocytes, so more are found in facial skin associated to the lower back and a greater number on the outer arm compared to the inner arm. The number of melanocytes is the same in equivalent body sites in white and black skin but the distribution and rate of production of melanin is different. Intrinsic ageing diminishes the melanocyte population. Merkel cells are also found in the basal layer with large numbers in touch sensitive sites such as the fingertips and lips. They are closely associated with cutaneous nerves and seem to be involved in light touch sensation.

Stratum spinosum
As basal cells reproduce and mature, they move towards the outer layer of skin, initially forming the stratum spinosum. Inter cellular bridges, the desmosomes, which appear as ‘prickles’ at a microscopic level, connect the cells. Langerhans cells are dendritic, immunologically active cells derived from the bone marrow, and are found on all epidermal surfaces but are mainly located in the middle of this layer. They play a important role in immune reactions of the skin, acting as antigen-presenting cells.

Stratum granulosum
Continuing their transition to the surface the cells continue to flatten, lose their nuclei and their cytoplasm appears granular at this level.

Stratum corneum
The final outcome of keratinocyte maturation is found in the stratum corneum, which is made up of layers of hexagonal-shaped, non-viable cornified cells known as corneocytes. In most areas of the skin, there are 10±30 layers of stacked corneocytes with the palms and soles having the most. Each corneocytes is surrounded by a protein envelope and is filled
with water-retaining keratin proteins. The cellular shape and orientation of the keratin proteins add strength to the stratum corneum. Surrounding the cells in the extracellular space are stacked layers of lipid bilayers (The resulting structure provides the natural physical and water-retaining barrier of the skin. The corneocytes layer can absorb three times its weight in water but if its water content drops below 10% it no longer remains pliable and cracks. The movement of epidermal cells to this layer usually takes about 28 days and is known as the epidermal transit time.

Fig 1: Cross section of skin

Dermis
The dermis varies in thickness, ranging from 0.6 mm on the eyelids to 3 mm on the back, palms and soles. It is found below the epidermis and is composed of a tough, supportive cell matrix. Two layers comprise the dermis:
- A thin papillary layer
- A thicker reticular layer.

The papillary dermis lies below and connects with the epidermis. It contains thin loosely arranged collagen fibers. Thicker bundles of collagen run parallel to the skin surface in the deeper reticular layer, which extends from the base of the papillary layer to the subcutis tissue. The dermis is made up of fibroblasts, which produce collagen, elastin and structural proteoglycans, together with immune competent mast cells and macrophages. Collagen fibers make up 70% of the dermis, giving it strength and toughness. Elastin maintains normal elasticity while proteoglycans provide viscosity and hydration. Rooted Aroma dermatology within the fibrous tissue of the dermis are the dermal vasculature, lymphatics, nervous cells and fibers, sweat glands, hair roots and small quantities of striated muscle.

Hypodermis
The hypodermis 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 being well integrated with the dermis through the nerve and vascular networks. The hypodermis layer is composed of loose connective tissues and its, thickness varies according to the surface of body.

Drug penetration pathways
There are critically three ways in which a drug molecule can cross the intact stratum corneum through the intercellular lipid domains; or by a transcellular route. A particular drug is likely to permeate by a combination of these routes, with the relative contributions of these pathways to the gross flux governed by the physicochemical properties of the molecule.

The appendageal route
Skin appendages offer a continuous channel directly across the stratum corneum barrier. However, their influence on drug penetration is hindered by number of factors. The surface area occupied by hair follicles and sweat ducts are small (typically 0.1% of skin’s surface area), therefore limiting the area available for direct contact of the applied drug formulation.

Transcellular route/ Intracellular route
Drugs entering the skin via the transcellular route pass through corneocytes. Corneocytes containing highly hydrate keratin provide an aqueous environment from which hydrophilic drugs can pass. The diffusion pathway for a drug via the transcellular route requires a number of partitioning and diffusion steps.

Intercellular route
The intercellular pathway involves drug diffusing through the continuous lipid matrix. This route is a significant obstacle for two reasons:
Recalling the ‘bricks and mortar’ model of the stratum corneum, the inter digitating nature of the corneocytes yields a tortuous pathway for intercellular drug permeation, which is in contrast to the relatively direct path of the transcellular route. The intercellular domain is a region of alternating structured bilayered consequently, a drug must sequentially partition into and diffuse through repeated aqueous and lipid domains. This route is generally accepted as most common path for small uncharged molecules penetrating the skin.
Physicochemical properties of penetrant

Partition coefficient
For molecules with intermediate partition coefficient (log P 1 to 3) and for highly lipophilic molecules (log P>3), the intercellular route will be almost the pathway used to traverse the stratum corneum. However, for these molecules a further consideration is the ability to partition out of the stratum corneum into the aqueous viable epidermal tissues. For more hydrophilic molecules (log P<1), the transcellular route probably predominates.

Molecular size
A second major factor in determining the flux of a material through human skin is the size of the molecule. However, for simplicity the molecular weight is generally taken as an approximation of molecular size. It has been suggested that an inverse relationship existed between transdermal flux and molecular weight of the molecule.

Solubility/melting point
It is well known that most organic materials with high melting points have relatively low aqueous solubility at normal temperature and pressure. The lipophilic molecules tend to permeate through the skin faster than more hydrophilic molecules. However, while lipophilicity is a desired property of transdermal candidates, it is also necessary for the molecule to exhibit some aqueous solubility since topical medicaments are generally applied from an aqueous formulation.

Ionization
According to pH-partition hypothesis, only the unionized forms of the drug can permeate through the lipid barrier in significant amounts.

Penetrant concentration
Assuming membrane related transport, increasing concentration of dissolved drug causes a proportional increase in flux. At concentration higher than the solubility, excess solid drug functions as a reservoir and helps maintain a constant drug constitution for a prolonged period of time.

Diffusion coefficient
Penetration of drug depends on diffusion coefficient of drug. At a constant temperature the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.

Other factors
Beyond the factors mentioned above, there are other molecular properties that can affect drug delivery through the skin. Drug binding is a factor that should be born in mind when selecting appropriate candidates. Interactions between drug substances and the tissue can vary from hydrogen bonding to weak Van der Waals forces and the effect of drug binding on flux across the tissue will vary depending on the permeant, e.g. with a poorly water soluble drug in an aqueous donor solution, significant binding to the stratum corneum may completely retard drug flux. Consequently, there will be a delay between applying a drug to the surface of the tissue and its appearance in a receptor solution (in vitro) or the blood (in vivo). Depending on the type of formulation selected, other factors may be important in a transdermal delivery system. For example, if the drug is suspended then the particle size may become a main regulator of flux.

Physicochemical properties of the drug delivery system

Release characteristics
Solubility of the drug in the vehicle determines the release...
rate. The mechanism of drug release depends on the following factors:
- Whether the drug molecules are dissolved or suspended in the delivery systems.
- The interfacial partition coefficient of the drug from the delivery system to the skin tissue.
- pH of the vehicle.

Composition of the drug delivery systems
The composition of the drug delivery systems, e.g. boundary layers, thickness, polymers, vehicles not only affects the rate of drug release, but also the permeability of the stratum corneum by means of hydration, making with skin lipids, or other sorption promoting effects.

Enhancement of Transdermal permeation
Majority of drugs will not penetrate skin at rates sufficiently high for therapeutic efficacy. In order to allow clinically useful transdermal permeation of most drugs, the penetration can be improved by the addition of a permeation promoter into the drug delivery systems.

Physiological factors
Skin properties in the neonate and young infant
The skin of newborns is known to be relatively susceptible to irritants, other variables related to stratum corneum function such as pH and stratum corneum hydration may enhance the irritant potential to newborn skin. Skin surface pH values in newborns are significantly higher in all body sites than those in adult skin, but stabilize at values similar to adults within the first month. There are also significant changes in the metabolic capacity of infants, whether full or preterm and adult levels of cutaneous enzyme activity are not observed until 2 months or even 6-12 months of age which may additionally account for the sensitivity of baby skin to irritants. The skin surface of the newborn is slightly hydrophobic and relatively dry and rough when compared to that of older infants. Stratum corneum hydration stabilizes by the age of 3 months.

Skin barrier properties in aged skin
There are changes in the physiology of aged skin (>65 years). The corneocytes are shown to increase in surface area which may have implications for stratum corneum function due to the resulting decreased volume of intercorneocyte space per unit volume of stratum corneum. The moisture content of human skin decreases with age. There is a flattening of the dermoepidermal junction and, consequently, the area available for diffusion into the dermis is diminished.

Race
Racial differences between black and white skins have been shown in some anatomical and physiological functions of the skin although data is relatively sparse. In black skin, increased intracellular cohesion, higher lipid content and higher electrical skin resistance levels compared to whites have been demonstrated.

Body site
It is readily apparent that skin structure varies to some degree over the human body. However, the relative permeability of different skin sites is not simply a function of stratum corneum thickness as different permeants exhibit varied rank orders through different skin sites. It is apparent that genital tissue usually provides the most permeable site for transdermal drug delivery. The skin of the head and neck is also relatively permeable compared to other sites of the body such as the arms and legs.

Skin temperature
The human body maintains a temperature gradient across the skin from around 37 °C to around 32 °C at the outer surface. Since diffusion through the stratum corneum is a passive process, elevation of the skin temperature can induce structural alterations within the stratum corneum, and these modifications can also increase diffusion through the tissue.

Skin condition
Acids and alkalis, many solvents like chloroform, methanol damage the skin cells and promote penetration. Diseased state of patient alters the skin conditions. The intact skin is better barier but the above mentioned conditions affect penetration.

Blood supply
Changes in peripheral circulation can affect transdermal absorption.

Skin metabolism
Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. Soskin metabolism determines efficacy of drug permeated through the skin.

Basic components of TDDS [16]
Polymer matrix/ Drug reservoir
Drug
Permeation enhancers
Pressure sensitive adhesive (PSA)
Backing laminates
Rate controlling membrane
Release liner
Other excipients like plasticizers and solvents

Polymer matrix
Polymers are the backbone of a transdermal drug delivery system. Systems for transdermal delivery are fabricated as multilayered polymeric laminates in which a drug reservoir or a drug polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and/or rate controlling membrane. Polymer selection and design must be considered when striving to meet the diverse criteria for the fabrication of effective transdermal drug delivery systems. The main challenge is in the design of a polymer matrix, followed by optimization of the drug loaded matrix not only in terms of release properties, but also with respect to its adhesion-cohesion balance, physicochemical properties, compatibility and stability with other components of the system as well as with skin.

The polymers utilized for TDDS can be classified as:

Natural polymers
cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber, chitosan, starch, etc.

Synthetic elastomers
polybutadiene, polyisobutylene, silicon rubber, nitrile, acrylonitrile, styrene-butadiene rubber, neoprene, butylrubber, polysiloxane, etc.
Synthetic polymers
polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, epoxy polymethylmethacrylate, ethyl cellulose, hydroxy propyl cellulose etc.
The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose and hydroxyl propyl methylcellulose are used as matrix formers for TDDS. Other polymers like EVA (Ethyl vinyl acetate), silicon rubber and polyurethane are used as rate controlling membrane.

Drug
The most important criteria for TDDS are that the drug should possess the right Physicochemical and pharmacokinetic properties. The selection of drug for transdermal drug delivery depends upon various factors.

Physicochemical properties
The drug should have some degree of solubility in both oil and water (Ideally greater than 1 mg/ml). The substance should have melting point less than 200°F. Concentration gradient across the membrane is directly proportional to the log solubility of drug in the lipid phase of membrane, which in turn is directly proportional to the reciprocal of melting point. Substances having a molecular weight of less than 600 units are suitable. A saturated aqueous solution of the drug should have a pH value between 5 to 9 and drugs highly acidic or alkaline in solution are not suitable for TDDS; because they get ionized rapidly at Physiological pH.

Biological properties
- The drug should have short biological half-life.
- Drug should be very potent, i.e., it should be effective in few mgs per day (Ideally less than 25 mg/day).
- Therapeutic index should be low.
- The drug should be non-irritant and non-allergic to human skin.
- The drug should be stable when in contact with the skin.
- The drug should not stimulate an immune reaction to the skin.
- Tolerance to drug must not develop under zero order release profile of transdermal delivery.
- The drug should not get irreversibly bound in the subcutaneous tissue.
- The drug should not get extensively metabolized in the skin.
- Drugs, which degrade in the GIT or are inactivated by hepatic first-pass effect, are suitable candidates for transdermal delivery.
- Drugs, which have to administer for a long period of time or which cause adverse effects to non-target tissues can also be formulated for transdermal delivery.

Permeation enhancers
Substances exist which temporarily diminish the impermeability of the skin are known as accelerants or sorption promoters or penetration enhancers. These include water, pyrrolidone, fatty acids and alcohols, azone and its derivatives, alcohols and glycols, essential oils, terpenes and derivatives, sulfoxides like dimethylsulfoximide (DMSO) and their derivatives, urea and surfactants.

Surfactants
These are proposed to enhance polar pathway transport especially of hydrophilic drugs. The ability of a surfactant to alter penetration enhancing of a drug.

Anionic surfactants
Sodium lauryl sulphate, Decodecylmethylsulphoxide, DMSO etc.

Nonionic surfactants
Pluronic F 127, Pluronic F68 etc.
Enhancer actions can be classified by lipid-protein partitioning concept. This hypothesis suggests that enhancers act by one or more ways selected from three main possibilities.

Lipid action
Some enhancers interact with the organized intracellular lipid structure of the stratum corneum so as to disrupt it and make it more permeable to drug molecules. Some solvents act by extracting the lipid components and thus make the horny layer more permeable.

Protein modification
Ionic surface active molecules in particular tend to interact well with the keratin in the corneocytes, to open up the dense keratin structure and make it more permeable. The intracellular route is not usually prominent in drug permeation, although drastic reductions to this route could open up an alternative path for drug penetration.

Partitioning promotion
Many solvents can enter the stratum corneum, change its solvent properties and thus increase the partitioning of a second molecule into the horny layer. This molecule may be a drug, a co enhancer or a co-solvent. e.g. Ethanol has been used to increase the penetration of the drug molecules nitroglycerin and estradiol.

Pressure sensitive adhesive (PSA)
A PSA is a material that helps in maintaining an intimate contact between transdermal system and the skin surface PSA is a material that adheres with no more than applied finger pressure, is aggressively and permanently tacky, exerts a strong holding force and should be removable from a smooth surface without leaving a residue. Adhesion involves a liquid-like flow resulting in wetting of the skin surface upon the application of pressure and when pressure is removed, the adhesive sets in that state. Acrylic-poly isobutylene- and silicone-based adhesives are used mostly in the design of transdermal patches. The selection of an adhesive is based on a number of factors, including the patch design and drug formulation. For reservoir systems with a peripheral adhesive, an incidental contact between the adhesive and the drug or penetration enhancers must not cause instability of the drug, penetration enhancer, or the adhesive. In the case of reservoir systems that include a face adhesive, the diffusing drug must not affect the adhesive. For matrix designs in which the adhesive, the drug and the penetration enhancers must be compounded, the selection will be more complex. The physicochemical characteristics of a drug adhesive combination- such as solubility and partition coefficient and adhesive characteristics such as the extent of crosslinking will determine the choice of adhesive for a drug. When formulating a PSA, a balance of four properties must be taken into account: tack, peel adhesion, skin adhesion and cohesive strength.
**Backing layer**
It protects the patch from the outer environment. The backing layer should be impermeable to drug and penetration enhancers. It does a function of holding the entire system and protects drug reservoir from atmosphere. The commonly used backing materials are polyesters, aluminized polyethylene terephthalate and siliconized polyethylene terephthalate.

**Rate controlling membrane**
Reservoir-type transdermal drug delivery systems contain an inert membrane enclosing an active agent that diffuses through the membrane at a finite controllable rate. The release rate controlling membrane can be nonporous so that the drug is released by diffusing directly through the material or the material may contain fluid-filled microspores, in which case the drug may additionally diffuse through the fluid, thus filling the pores. In the case of nonporous membranes, the rate of passage of drug molecules depends on the solubility of the drug in the membrane and the membrane thickness. Hence, the choice of membrane material must conform to the type of drug being used. By varying the composition and thickness of the membrane, the dosage rate per area of the device can be controlled.

**Release liner**
During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than apart of dosage form for delivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water.

Typically, release liner is composed of a base layer which may be non-occlusive or occlusive and a release coating layer made up of silicon or Teflon. Other materials used for TDDS release liner include polyester foil and metalized laminates.

**Plasticizer and solvents**

**Plasticizer**
In transdermal systems, plasticizers are used to improve the brittleness of the polymer and to provide flexibility. They are generally non-volatile organic liquids or solids with low melting temperature and when added to polymers, they cause changes in definite physical and mechanical characteristics of the material. Upon addition of plasticizer, flexibilities of polymer macromolecules or macromolecular segments increase as a result of loosening of tightness of intermolecular forces. Many of polymers used in pharmaceutical formulations are brittle and require the addition of plasticizer into the formulation. The plasticizers with lower molecular weight have more molecules per unit weight compared to the plasticizers with higher molecular weight. These molecules can more easily penetrate between the polymer chains of the film forming agent and can interact with the specific functional groups of the polymer. By adding plasticizer to a polymeric material, elongation at break, toughness and flexibility are expected to increase; on the other hand, tensile stress, hardness, electrostatic chargeability, and glass transition temperature ($T_g$) are expected to decrease.

**Solvents**
Various solvents are used to solve or disperse the polymer and adhesive or drug used in preparation of transdermal system. Among those chloroform, methanol, acetone, isopropanol and dichloromethane are used frequently.
Types of Transdermal Patch \[34\]

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

The adhesive layer of this system also contains the drug. In this type of patch, the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

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

The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. The multi-layer system is different however that it adds another layer of drug-in -adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing.

**Reservoir**

Unlike the Single-layer and Multi-Layer Drug, inadhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system, the rate of release is zero order.

**Matrix**

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

**Vapour Patch**

In this type of patch, the adhesive layer not only serves to adhere the various layers together but also to release vapor. The vapor patches are new on the market and they release essential oils for up to 6 hours. The vapors patches release essential oil sand is used in cases of decongestion mainly. Other vapor patches on the market are controller vapor patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market.

**Care taken while applying Transdermal patch**

1. The part of the skin where the patch is to be applied should be properly cleaned.
2. Patch should not be cut because cutting the patch destroys the drug delivery system.
3. Before applying a new patch it should be made sure that the old patch is removed from the site.
4. Care should be taken while applying or removing the patch because anyone handling the patch can absorb the drug from the patch.
5. The patch should be applied accurately to the site of administration.

**Permeation enhancement techniques \[16\]**

The method employed for modifying the barrier properties of the stratum corneum to enhance drug permeation and absorption through skin may be classified into the following categories

1. Chemical enhancement techniques
2. Physical enhancement techniques
3. Vesicular carriers
4. Miscellaneous techniques
5. Carriers/vehicles

Chemical enhancement techniques
The use of Chemical permeation enhancers (CPEs) over the other techniques has certain advantages, including design flexibility of the patch and ease of patch application over a large area (>10 cm²). An ideal penetration enhancer should reversibly reduce the barrier resistance of the Stratum corneum without damaging the skin cells. Ideal penetration enhancers should possess the following properties:
- Pharmacologically inert
- Nontoxic, non-irritating, and non-allergic
- Rapid onset of action; predictable and suitable duration of action for the drug used
- Reversible effect of the CPE on the barrier property of SC
- Chemically and physically compatible with the delivery system
- Readily incorporated into the delivery system
- Inexpensive and cosmetically acceptable

Because the skin provides such a tough barrier to the delivery of most drugs, a broad range of changed chemical additives have been tested to increase transdermal penetration during the last two decades. Much of the cited literature is found in patents as well as pharmaceutical science literature. Even though many chemical entities have been recognized, only a few were introduced in the market due to several limitations, which include their economic feasibility and the toxic effects on skin, which make them undesirable for developing transdermal patches.

Mechanism of chemical penetration enhancement
Penetration enhancers may act by one or more of three main mechanisms:
1. Disruption of the highly ordered structure of stratum corneum lipid.
2. Interaction with intercellular protein.
3. Improved partition of the drug, co enhancer or solvent into the stratum corneum.

The enhancer act by altering one of three pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The fatty acid enhancers increased the fluidity of the lipid protein portion of the stratum corneum. Some enhancers act on both polar and non-polar pathways by altering the multi laminate pathway for penetration. Enhancers can increase the drug diffusivity through skin proteins. The type of enhancer employed has a significant impact on the design and development.

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\frac{dm}{dt} = DC_0K/h
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If we plot the cumulative mass of diffusant, m, passing per unit area through the membrane, at long time the graph approaches linearity and its, slope its yield the steady flux, where Co is the constant concentration of drug in donor solution, K is the partition coefficient of the solute between the membrane and the bathing solution, D is the diffusion coefficient and h is thickness of membrane. From the above equation, we deduce the ideal properties of a molecule that would penetrating stratum corneum well. These are:
- Low molecular mass, preferably less than 600Daltons.
- Adequate solubility in oil and water so that membrane concentration gradient may be high.

Sulphoxides and similar chemicals
Dimethyl sulphoxides (DMSO) is one of the earliest and most widely studied penetration enhancers. It is a powerful solvent which hydrogen bonds with itself rather than with water. It is colourless, odourless and is hydroscopic and is often used in many areas of pharmaceutical sciences as a “universal solvent”. DMSO alone has been applied topically to treat systemic inflammation. DMSO works rapidly as a penetration enhancer - spillage of the material onto the skin can be tasted in the mouth within a second. Although DMSO is an excellent accelerant, it does create problems. The effect of the enhancer is concentration-dependent and generally cosolvents containing > 60% DMSO are needed for optimum enhancement efficacy. However, at these relative high concentrations, DMSO can cause erythema of the stratum corneum. Denaturing of some skin proteins results in erythema, scaling, contact urticaria, stinging and burning sensation. Since DMSO is problematic for use as a penetration enhancer, researchers have investigated a similar chemically-related material as a accelerant. Dimethylacetamide (DMAC) and dimethylformamide (DMF) are similarly powerful solvents. However, Southwell and Barry, showing a 12-fold increase in the flux of caffeine permeating across a DMF-treated human skin, concluded that the enhancer caused irreversible membrane damage. DMF irreversibly damages human skin membranes but has been found in vivo to promote the bioavailability of betamethasone-17-benzoate as measured by vasoconstrictor assay. DMSO may also extract lipids, making the horny layer more permeable by forming aqueous channels. It has been postulated that DMSO denatures the intercellular structural proteins of the stratum corneum, or promotes lipid fluidity by disruption of the ordered structure of the lipid chains. In addition, DMSO may alter the physical structure of the skin by elution of lipid, lipoprotein and nucleoprotein structures of the stratum corneum. Decymethylsulfoxide (DCMS) is thought to promote permeation enhancement as a result of protein-DCMS interaction creating aqueous channels, in addition to lipid interactions.

Alkanes
Long chain alkanes (C7-C16) have been shown to enhance skin permeability by non-destructive alteration of the stratum corneum barrier.

Azone
Azone (1-dodecylazacycloheptan-2-one or laurocapran) was the first molecule specifically designed as a skin penetration enhancer. Azone is a colourless, odourless liquid with a melting point of -7 ºC and it possesses a smooth, oily but yet non-greasy feel. Azone is a highly lipophilic material with a log p octanol / water of around 6.2 and it is soluble in and compatible with most organic solvents including alcohol and propylene glycol. Azone enhances the skin transport of a wide variety of drugs including steroids, antibiotics and antiviral agents. Azone is most effective at low concentrations, being employed typically between 0.1-5 % but more often between 1-3%. Azone partitions into a bilayer lipid to disrupt their
packing arrangement but integration into the lipid is unlikely to be homogeneous. Azone aggravates dynamic structural disorder of the intercellular lamellar lipid structure all through the stratum corneum and the design of fluid domains containing the intercellular lipids, which was recommended by 2H NMR assay. Another mechanism was also projected based on the alteration of the lateral bonding within stratum corneum lipid lamellae. Azone increase penetration through the stratum corneum by affecting both the hydrophilic and lipophilic routes of penetration. Azone increases the fluidity of the lipid layer.

**Pyrrolidones**

Pyrrolidones have been used as permeation enhancers for numerous molecules including hydrophilic (e.g. mannitol and 5-flourouracil) and lipophilic (progesterone and hydrocortisone) permeants. N-methyl-2- pyrrolidone was employed with limited success as a penetration enhancer for captopril when formulated in a matrix-type transdermal patch. The pyrrolidones partition well into human stratum corneum within the tissue and they may act by altering the solvent nature of the membrane. Pyrrolidones have been used to generate reservoirs within the skin membrane. Such a reservoir effect offers a potential for sustained release of a permeant from the stratum corneum over extended time periods.

**Urea**

Urea promotes transdermal permeation by facilitating hydration of the stratum corneum and by the formation of hydrophilic diffusion channels within the barrier. As urea itself possesses only borderline penetration enhancing activity, attempts have been made to synthesis analogues containing more potent enhancing moieties.

**Fatty acids and Esters**

Percutaneous drug absorption has been increased by a wide variety of fatty acids and their esters, the most popular of which is oleic acid. A general trend has been seen that unsaturated fatty acids are more effective in enhancing percutaneous absorption of drugs than their saturated counterparts. It is of interest to note that many penetration enhancers such as azone contain saturated or unsaturated hydrocarbon chains and some structure-activity relationships have been drawn from the extensive studies of Aungst who employed a range of fatty acids, acids, alcohols, sulphoxides, surfactants and amides as enhancers for naloxone. Shin, et, al. studied various penetration enhancers like glycols (diethylene glycol and tetraethylene glycol), fatty acids (lauric acid, myristic acid and capric acid) and non-ionic surfactant (polyoxyethylene-2-oleyl ether, polyoxy ethylene-2-stearly ether) on the release of triprolidone. Lauric acid in Propylene glycol enhanced the delivery of highly lipophilic antiestrogen. Oleic acid greatly increased the flux of many drugs such as increasing the flux of salicylic acid 28-fold and 5-flourouracil flux 56-fold through human skin membrane in vitro. The enhancer interacts with and modifies the lipid domains of the stratum corneum as would be expected for a long chain fatty acid with cis- configuration.

**Alcohols, fatty alcohols and glycols**

Alcohols may stimulate transdermal penetration by a number of mechanisms. The alkyl chain length of the alkanols (fatty alcohols) is an important parameter in the promotion of permeation enhancement. Augmentation appears to increase as the number of carbon units increases, up to a limiting value. In addition, lower molecular weight alkanols are thought to act as solvents, enhancing the solubility of drugs in the matrix of the stratum corneum. Disruption of the stratum corneum integrity through extraction of biochemically by the more hydrophobic alcohols almost certainly also contributes to enhanced mass transfer through this tissue. Ethanol is the most commonly used alcohol as a transdermal penetration enhancer. Ethanol acts as a penetration enhancer by extracting large amounts of stratum corneum lipids. It also increases the number of free sulphhydryl groups of keratin in the stratum corneum proteins. Usually, pretreatment of skin with ethanol increases the permeation of hydrophilic compounds, while it decreases that of hydrophobic ones. The molecular complexity of different glycol molecules is a determinant of their efficacy as permeation enhancers. Solubility of the drug in the delivery vehicle is markedly influenced by the number of ethylene oxide functional groups on the enhancer molecule; this solubility modification may either enhance or retard transdermal flux depending on the specific drug and delivery environment. The activity of propylene glycol (PG) is thought to result from solvation of α keratin within the stratum corneum; the occupation of proteinaceous hydrogen bonding sites reducing drug-tissue binding and thus promoting permeation. PG is widely used as a vehicle for penetration enhancers and shows synergistic action when used with, for example, oleic acid.

**Surfactants**

Many surfactants are capable of interacting with the stratum corneum to increase the absorption of drugs and other active compounds from products applied to the skin. Skin penetration measurements are valuable in quantifying these effects and observing the influence of surfactant chemistry and concentration. A surfactant interacts with skin by depositing onto the stratum corneum, thereby disorganizing its structure. Then surfactant can solubilise or remove lipids or water-soluble constituents in or on the surface of the stratum corneum. Finally, it can be transported into and through the stratum corneum. This last effect is related to the surfactant and stratum corneum protein interaction and epidermal keratin denaturation. In general, anionic surfactants are more effective than cationic and non-ionic surfactants in enhancing skin penetration of target molecules. Some anionic surfactants interact strongly with both keratin and lipids, whereas the cationic surfactants interact with the keratin fibrils of the cornified cells and result in a disrupted cell-lipid matrix. Non-ionic surfactants enhance absorption by inducing fluidization of the stratum corneum lipids. Scheuplein and Ross reported that the capacity of the stratum corneum to retain significant quantities of membrane-bound water is reduced in the presence of sodium dodecaneato and sodium dodecyl sulfate. This effect is readily reversible upon removal of the agents. These investigations proposed that anionic surfactants alter the permeability of the skin by acting on the helical filaments of the stratum corneum, thereby resulting in the uncoiling and extension of keratin filaments to produce keratin. Then they cause an expansion of the membrane, which increases permeability. However, more recent findings suggest that impairment of the skin’s barrier properties is unlikely to result from changes in protein conformation alone. Based on differential scanning calorimetry results, sodium lauryl sulfate (SLS) disrupted both the lipid and the protein components. The amount of surfactant that penetrates the skin
after the disruption of the skin barrier depends on the monomer activity and the critical micelle concentration (CMC). Above the CMC, the added surfactant exists as micelles in the solution and micelles are too large to penetrate the skin. The extent of barrier disruption and penetration enhancement of a surfactant is also strongly dependent on surfactant structure, especially alkyl chain length. In general, studies have shown that surfactants having 12 carbons in their alkyl chain cause more disruption to the skin barrier and allow drugs to penetrate more readily than those that have more or less than 12 carbons. The explanation for this optimum of 12 carbons is not known yet.

**Essential oil, terpenes and terpenoids**

Terpenes are found in essential oils, and are compounds comprising of only carbon, hydrogen and oxygen atoms, but which are not aromatic. Numerous terpenes have long been used as medicines as well as flavoring and fragrance agents. The essential oils of eucalyptus, chenopodium, ylang-ylang has been found to be effective penetration enhancers for 5-fluorouracil traversing human skin in vivo. Cornwell et al. investigated the effect of 12 sesquiterpenes on the permeation of 5-fluorouracil in human skin. Pretreatment of epidermal membranes with sesquiterpene oil or using solid sesquiterpenes saturated in dimethyl isosorbide increased the absorption of 5-fluorouracil.

L-menthol has been used to facilitate in vitro permeation of morphine hydrochloride through hairless rat skin as well as diffusion of imipramine hydrochloride across rat skin and hydrocortisone through hairless mouse skin. One mechanism by which this agent operates is to modify the solvent nature of the stratum corneum, thus improving drug partitioning into the tissue. Many terpenes permeate human skin well and large amounts of terpene have been found in the epidermis after application from a matrix-type patch. Terpenes may also modify drug diffusivity through the membrane. During steady state permeation experiments using terpenes as penetration enhancers, the lag time for permeation was usually reduced, indicating some increase in drug diffusivity through the membrane following terpene treatment.

**Cyclodextrins**

Cyclodextrins are biocompatible substances that can form inclusion complexes with lipophilic drugs with a resultant increase in their solubility, particularly in aqueous solutions. However, cyclodextrins alone were determined to be less effective as penetration enhancers than when combined with fatty acids and propylene glycol.

**Oxazolidinones**

Oxazolidinones are a new class of chemical agents which have the potential for use in many cosmetic and personal care product formulations. This is due to their ability to localize co-administered drug in skin layers, resulting in low systemic permeation. The structural features of these permeation enhancers are closely related to sphingosine and ceramide lipids which are naturally found in the upper skin layers. Oxazolidinones such as 4-decyloxazolidin-2-one has been reported to localize the delivery of many active ingredients such as retinoic acid and diclofenac sodium in skin layers. This compound has a higher molecular weight and lipophilicity than other solvent-type enhancers, physical characteristics that may be beneficial in terms of a reduction in local toxicity because of the lack of effective absorption of these enhancers into the lower skin layers where irritation is likely to be occur.

**Physical enhancement techniques**

The various classes of active systems under development includes Iontophoresis, Electrophoresis, Micro needles, needle less injection, stretching, ultrasound, magnetophoresis, radio frequency, lasers, photomechanical waves and temperature manipulation. Some most commonly employed techniques include the following.

**Iontophoresis**

Iontophoresis passes a few milli amperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. Mainly used of pilocarpine delivery to induce sweating as part of cystic fibrosis diagnostic test. Iontophoretic delivery of lidocaine appears to be a promising approach for rapid onset of anesthesia.
Application by ultrasound
Application of ultrasound, particularly low frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules. It is also known as sonophoresis. Katz et al., reported on the use of low-frequency sonophoresis for topical delivery of EMLA cream.

Use of microscopic projection
Transdermal patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. Needles ranging from approximately 10-100 µm in length are arranged in arrays. When pressed into the skin, the arrays make microscopic punctures that are large enough to deliver macromolecules, but small enough that the patient does not feel the penetration or pain. The drug is surface coated on the microneedles to aid in rapid absorption. They are used in development of cutaneous vaccines for tetanus and influenza. Various other methods are also used for the application of the transdermal patches like thermal poration, magnetophoresis, and photomechanical waves. However, these methods are in their early stage of development and required further detail studying.

Vesicular carriers
Liposomes and other vesicles
Liposomes are colloidal particles moulded as concentric bimolecular layers that are capable of encapsulating drugs. Liposomes acts by penetrating the epidermis, carrying the drug into skin and those large multilamellar vesicles could lose their external bilayer during penetration and these liposome lipids penetrate into the stratum corneum by adhering onto the surface of the skin and, successively destabilizing, and fusing or mixing with the lipid matrix. Thereafter, they may act as penetration enhancers, loosening the lipid structure of the stratum corneum and promoting reduced barrier function of these layers to the drug, with less well-packed intercellular lipid structure forms, and with subsequent increased skin partitioning of the drug. Studies have focused on delivery of agents via liposomes like anti-psoriatic agent via ethanolic liposomes, caffeine for hyperproliferative diseases.

Niosomes
Niosomes are vesicles composed of non-ionic surfactants that have been evaluated as carriers for a number of drug and cosmetic applications. In fact, if compared with conventional liposomes (phospholipids) niosomes (non-ionic surfactant vesicles) offer higher chemical stability, lower costs, and great availability of surfactant classes. Niosomes seems an interesting drug delivery system in the treatment of dermatological disorders. In fact, topically applied niosomes can increase the residence time of drugs in the stratum corneum and epidermis, while reducing the systemic absorption of the drug. They are thought to improve the horny layer properties; both by reducing trans epidermal water loss and by increasing smoothness viarefilling lost skin lipids.

Transfersomes
These are vesicles composed of phospholipids as their main ingredient with 10-25% surfactant and 3-10% ethanol. Liposomes are too large to pass through pores of less than 50nm in size; transfersomes up to 500nm can squeeze to penetrate the stratum corneum barrier spontaneously. The driving force for penetration into the skin is the “Transdermal gradient” caused by the difference in water content between the restively dehydrated skin surface (approximately 20% water) and the aqueous viable epidermis. Studies have been focused on delivery of agents like vaccines, retinyl palmitate, estradiol, copper, zinc, superoxide dismutase, insulin. In some cases, the transfersomes drug delivery with some physical enhancement method iontophoresis for estradiol and microneedles for docetaxel.

Miscellaneous techniques
Selection of correct drug or prodrug
Drug should be selected in such a way that it fits in the criteria of transdermal delivery. The prodrug approach has been investigated to enhance dermal and transdermal delivery of drugs with unfavourable partition coefficients. The prodrug design strategy generally involves addition of a promoiety to increase partition coefficient and hence solubility and transport of the parent drug in the stratum corneum. Upon reaching the viable epidermis, esterases release the parent drug by hydrolysis thereby optimizing solubility in the aqueous epidermis. The intrinsic poor permeability of the very polar 6- mercaptopurine was increased up to 240 times using S-6- acyloxymethyl and 9- dialkylaminomethyl promoieties.

Chemical potential adjustment
The maximum skin penetration rate is obtained when a drug is at its highest thermodynamic activity as is the case in a supersaturated solution. The diffusion of paraben from saturated solutions in eleven different solvents through a silicone membrane was determined. Due to the different solubility of the parabens in the various solvents, the concentration varied over two orders of magnitude. However, paraben flux was the same from all solvents, as the...
thermodynamic activity remained constant because saturated conditions were maintained throughout the experiment. Supersaturated solutions can occur due to evaporation of solvent or by mixing of cosolvents. Clinically, the most common mechanism is evaporation of solvent from the warm skin surface, which probably occurs, in many topically applied formulations. In addition, if water is imbibed from the skin into the vehicle and acts as an anti-solvent, the thermodynamic activity of the permeant would increase.

**Ion pairs and complex coacervates**
Charged drug molecules do not readily partition into or permeate through human skin. Formation of lipophilic ion pairs has been investigated to increase stratum corneum penetration of charged species. This strategy involves adding an oppositely charged species to the charged drug, forming an ion-pair in which the charges are neutralised so that the complex can partition into and permeate through the stratum corneum. The ion-pair then dissociates in the aqueous viable epidermis releasing the parent charged drug, which can diffuse within the epidermal and dermal tissues.

**Eutectic systems**
The melting points of a drug influences solubility and hence skin penetration. According to regular solution theory, the lower the melting point, the greater the solubility of a material in a given solvent, including skin lipids. The melting point of a drug delivery system can be lowered by formation of a eutectic mixture, a mixture of two components which, at a certain ratio, inhibit the crystalline process of each other, such that the melting point of the two components in the mixture is less than that of each component alone. A number of eutectic systems containing a penetration enhancer as the second components have been reported, for example: Ibuprofen with terpenes, and methyl nicotinate, propanolol with fatty acids, and lignocaine with menthol.

**Vehicles/carriers**

**Micro or nanocapsules**
These are composed of multiple concentric bilayers of surfactant; separated by a polar liquid medium, generally in water in which the hydrophilic additives can be in corporate. Their lipid core allows encapsulation of lipid additives and their multi-lamellar (lipid/water) structure creates good skin affinity leading to cutaneous penetration and good hydration.

**Nano emulsions/submicron emulsion (SME’S)/Mini emulsions**
These are oil in water emulsions with an average droplet size ranging from 100 to 500nm. They have very good stability and they do not undergo phase separation during storage. They have a liquid lipophilic core and are appropriate for lipophilic compound separation.

**Solid lipid nano particles (SLN’s)**
These droplets are made by solid lipids. Their sizes range from 500-1000nm. They can be stabilized by surfactants or polymers. There are mainly 3 structures: Homogenous matrix, drug enriched shell, and drug enriched core. They can protect active components against chemical degradation and modulate compound release. SLN’S also possess occlusive properties because of formation of a film on the skin. The film formed by lipid fusion is supposed to be a pore-less film with improved skin hydration and protection properties.

**Multiple emulsions**
These W/O/W emulsions consist in the dispersion of a W/O emulsion in an aqueous phase under several conditions. One can incorporate water-soluble ingredients and oil soluble additives. They substances can be protected and released sustained by controlling droplet breakdown. These systems can have high oily phase.

**Micro emulsions**
These formulations have been shown to be superior for cutaneous delivery compared to other conventional vehicles. These systems are identified as transparent mixtures of water, oil and surfactants. They are thermodynamically stable and optically isotropic. Micro emulsions are spontaneously produced in a narrow range of oil-water-surfactant composition, represented on pseudo-ternary diagram phases. These are dynamic systems with transdermal delivery properties could be attributed to their excellent solubilising properties. Their high solubilising properties improve bio dispensability and thus reduce the efficient dose thereby increasing tolerability. Furthermore, they have an ability to restructure the skin and hair make micro emulsion formulations adapt to altered skin and hair conditions.

**Transdermal work done**
Y. Madhusudhan Rao et al., Developed Carvedilol Transdermal patches and evaluated for Physico-chemical, ex-vivo mechanical properties using different ratios of HPMC, HPC, ERS 100, and 8% v/w d-limonene as penetration enhancer and 20% w/w dibutyl phthalate as plasticizer and the results are found that the formulation containing HPMC E15cps: ERL 100 in 4:1 ratio showed maximum drug release in 24hrs.

Ramesh Gannu et al., Developed Matrix type Transdermal Drug Delivery System of Nitrendipine using blends of HPMC E 15cps and Eudragit RL 100 in different ratios using 6% Carvone as penetration enhancer and 15% propylene glycol as plasticizer and found that the patches consisting of Eudragit RL-100 and HPMC E15cps in the ratios of 2:3 and 1:4 showed maximum drug release.

M. Aqil et al., Formulated matrix type drug delivery systems of Pinacidil Monohydrate by film casting method on mercury substrate and evaluated in vitro prior to this work, the TDDS was composed of polymers Eudragit RL 100, and PVP K-30 in different ratios along with 20% w/w of Drug; Pinacidil monohydrate, 5% w/w of plasticizer, polyethylene glycol-400, and 5% w/w of penetration enhancers, dimethyl sulfoxide. The films were evaluated in vivo for drug permeation. The results indicate that increasing the quantity of ERL100 upto 60% w/w leads to an increment in the rate and extent of drug absorbed and extent of drug absorbed and higher % reduction in blood pressure.

**Evaluation of transdermal patches**
- Physicochemical evaluation
- In vitro evaluation
- In vivo evaluation

**I. Physicochemical Evaluation**

**Thickness**
The thickness of Transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometre at different points of the film. The average reading is calculated.
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.

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 hrs in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution. Concentration of drug is calculated by using standard graph.

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.

Moisture content
The prepared films are weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24 hrs. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula.

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

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

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

Flatness
A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

\[
\text{% constriction} = \frac{I2 - I1}{I1} \times 100
\]

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.

\[
\text{Tensile strength}\text{=}\frac{F}{a.b} \times \left(1 + \frac{L}{l}\right)
\]

\[
F \text{ is the force required to break; } a \text{ is width of film; }
\]

\[
b \text{ is thickness of film; } L \text{ is length of film; }
\]

\[
l \text{ is elongation of film at break point.}
\]

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.

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

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

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

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

In vitro release studies
The paddle over disc
(USP apparatus 5) 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.

The Cylinder modified USP Basket
(USP apparatus 6). 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.

The reciprocating disc
(USP apparatus 7) In this method patches attached to holders are oscillated in small volumes of medium, allowing the apparatus to be useful for systems delivering low concentration of drug. In addition, paddle over extraction cell method 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 (KC) 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, sample analysis and calculation of flux i.e., drug permeated per cm² per sec.

**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 600 rpm. The system is controlled by thermostatic water through a water jacket surrounding the two compartments.

**Franz diffusion cell**

The cell is composed of two compartments: donor and receptor. The receptor compartment has a volume of 12 ml and effective surface area of 4.90 cm². The diffusion buffer is continuously stirred at 600rpm by a magnetic bar. The temperature in the bulk of the solution is maintained by continuously stirred at 600rpm by a magnetic bar. The cell is divided in receptor compartment has a volume of 12 ml and effective surface area of 4.90 cm². The diffusion buffer is continuously stirred at 600rpm by a magnetic bar. The temperature in the bulk of the solution is maintained by continuous stirring at 600rpm by a magnetic bar.

**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.

**In vivo Studies**

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

**Animal models**

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

**Human models**

The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug.

<table>
<thead>
<tr>
<th>Product name</th>
<th>Drug</th>
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<td>Scopolamine</td>
<td>Alza/Novartis</td>
<td>Motion sickness</td>
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<td>Grunenthal</td>
<td>Pain associated with post herptic neuralgia</td>
</tr>
<tr>
<td>Tolubutrol</td>
<td>Hokumalin</td>
<td>Abbott japan</td>
<td>Bronchial asthma</td>
</tr>
<tr>
<td>Orto evra</td>
<td>Estradiol</td>
<td>Orthro-Mencil Phrmecs</td>
<td>Birth control</td>
</tr>
<tr>
<td>Prostep</td>
<td>Nicotine</td>
<td>Elan corp</td>
<td>smoking cessation</td>
</tr>
<tr>
<td>Deponit</td>
<td>Nitro glycerine</td>
<td>Schwarz pharma</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Combipatch</td>
<td>Estradiol</td>
<td>Noven Inc/ Aventis</td>
<td>Hormone replacement therapy</td>
</tr>
</tbody>
</table>

Table 1: List of marketed Transdermal products
Conclusion
The transdermal drug delivery system (TDDS) has great potential for delivery of the drug on both hydrophilic and hydrophobic. It has been designed as an alternative safety and very feasible route for systemic drug delivery with permeation enhancers (physical, chemical) transdermal route is suitable for the patients, who are bedridden unconscious. Many new researchers are going on in present day to incorporate newer drug via this system which enhances modular drug delivery, novel carriers’ systems: microemulsion, nanoemulsion, liposomes, ethosomes, niosome can also be incorporated into the transdermal patch, which shows the important of formulation for better therapeutics action with prolonged effect. Transdermal drug delivery system is an alternative and promising way to systemic administration of drugs with and without permeation enhancers. The present article is to give information about the research work done so far, structure of skin, permeation enhancers (Physical and chemical) techniques of delivery and evaluation studies.

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References


