# TRANSDERMAL PATCH: RECENT ADVANCEMENT

**Abstract**

In recent years, a remarkable evolution has been seen in topical drug delivery systems that offer efficient and targeted delivery avenues. This chapter on topical drug delivery systems explores various innovative approaches and their diverse applications in healthcare. After briefly introducing the skin's role as a barrier and challenges associated with topical drug delivery, the chapter examines the mechanisms and principles behind creams, gels, ointments, patches, and nanoparticles. Nanoemulsions, liposomes, and microneedles are discussed as formulation strategies to enhance drug permeation and efficacy. It also discusses the importance of transdermal drug delivery for systemic effects and site-specific delivery for dermatological conditions. It also examines the integration of nanotechnology, microfluidics, and 3D printing into next-generation topical delivery systems. Topical formulations are clinically relevant and therapeutically effective across various medical disciplines, as illustrated by case studies and examples of successful formulations. As discussed in this chapter, topical drug delivery systems are essential for improving patient outcomes and optimizing drug therapy. The chapter also highlights the significance of site-specific delivery for dermatological conditions, wound healing, and transdermal drug delivery for systemic effects. Additionally, it explores the integration of novel technologies like nanotechnology, microfluidics, and 3D printing in designing next-generation topical delivery systems. Moreover, the chapter examines the regulatory considerations, safety profiles, and market trends shaping the landscape of topical drug delivery. This chapter provides a comprehensive overview of topical drug delivery systems, elucidating their pivotal role in optimizing drug therapy and improving patient outcomes.

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# I. INTRODUCTION

The application of medication directly to the skin to treat skin conditions is referred to as topical drug delivery, commonly used for localized skin infections or when systemic drugs are not suitable. The skin, being the largest organ in the human body, covers an average area of 2m2 and contains a significant portion of the body's circulating blood. Controlled drug delivery through the skin has gained importance in the pharmaceutical industry in recent decades, as the skin surface has numerous hair follicles and sweat ducts that affect drug penetration. Skin acts as a protective barrier, allowing only limited quantities of drug molecules to pass through gradually [1].

The Stratum corneum, with its lipid-rich composition and low water content, poses a challenge for the transportation of hydrophilic or charged molecules. Comprising approximately 40% lipids, 40% protein, and only 20% liquid, this surface restricts the movement of such molecules. However, lipophilic drug molecules can navigate through the Stratum corneum cells by breaking down into intercellular lipids. On the other hand, hydrophilic molecules have the potential to be absorbed into the skin through the limited 'pores' or openings of hair follicles and sebaceous glands. Nevertheless, these openings account for just 1% of the total skin surface, thereby restricting the absorption of medicines to a small area.

Topical drug delivery systems are crucial for ensuring that drug molecules are absorbed effectively and efficiently into the body. The absorption of these molecules through the skin is a key factor in achieving consistent therapeutic rates over time. The movement of drug molecules through the corneal barrier to deeper dermal layers and systemic absorption is a rapid process, especially for drugs with lipophilic properties. These properties make them ideal for topical delivery systems, ensuring that the drug reaches its intended location within the body. By applying these preparations to the skin surface, both regional and systemic effects can be achieved, allowing for the safe and effective delivery of lower-dose drug molecules compared to traditional methods. This targeted delivery reduces the risk of side effects and enhances patient adherence to treatment regimens. Dermatological disorders, such as skin diseases, have become increasingly prevalent in the population, leading to a rise in healthcare expenditure. This has driven the development of advanced topical formulations and drug delivery systems to address these conditions effectively. Recent advancements in life sciences have paved the way for innovative approaches to enhancing the delivery of topical dermatological agents, including the use of various technologies such as liposomes, bio-polymers, particulate carriers, occlusion methods, topical peels, sprays, foams, and even temperature and ultrasound-based techniques. These developments aim to improve the efficacy and safety of topical drug delivery systems for better patient outcomes. Novel delivery techniques represent a significant progression from conventional forms such as creams, lotions, ointments, and pastes, offering potential enhancements in efficacy, tolerability, patient compliance, and overall quality of life in dermatology. These innovative methods are poised to address specific needs within the topical dermatology field [2]. Despite the promising outlook, the formidable barrier properties of the skin present a formidable obstacle to achieving optimal dermal and transdermal delivery of various small and large molecules. This challenge underscores the importance of continued research and development efforts to overcome such limitations and maximize the potential benefits of advanced delivery systems.

## II. ADVANTAGES OF THE TOPICAL DRUG DELIVERY SYSTEM

- Prevent metabolism of the first step.
- Quick and easy to use for self-administration.
- Avoid intravenous therapy risks and inconveniences and different absorption conditions such as pH changes, enzyme activity, and gastric emptying period.
- Preparations of this type of product are easy.
- Delivering medicinal products more selectively to a specific site.
- Avoiding gastrointestinal incompatibility.
- Providing use of medicinal products with short biological half-life, small therapeutic window.
- Enhanced patient compliance.
- Provide suitability for self-medication.
- Effectiveness with lower total daily intake of medicinal products by continuous intake of medicinal products.
- Prevent changes in drug rates, and inter- and intra-patient variability.
- Distribution capacity through the topical route is more than a buccal or nasal cavity.
- Administration of drugs through this route is more target-specific [3].
- Disadvantages of the topical drug delivery system
- Skin irritation or dermatitis may occur due to the medication or excipients.
- Poor permeability of certain drugs through the skin.
- Drugs with a larger particle size cannot easily be absorbed through the skin.
- Risk of allergic reactions.
- Can only be used for medications that need very low levels of plasma for action.

## III. NATURAL POLYMER USED IN TRANSDERMAL PATCH

The transdermal method for drug delivery relies heavily on the use of polymers, which play a crucial role in regulating the release of the drug from the system. Polymers are large molecules made up of repeated structural units, and they are typically held together by covalent chemical bonds [4]. These polymers are essential in reducing the frequency of dosing and improving the effectiveness of the drug by ensuring targeted delivery to the site of action. They can be classified as natural, semi-synthetic, or synthetic, depending on their origin [5]. In pharmaceutical formulations, plant-derived polymers are commonly used to create solid monolithic matrix systems, plates, films, beads, microparticles, nanoparticles, inhalable and injectable systems, as well as viscous liquid formulations [6]. Within these dosage forms, polymers serve various functions such as binders, matrix formers, drug release regulators, film coating formers, thickeners, viscosity enhancers, stabilizers, disintegrates, solubilizers, emulsifiers, suspenders, gelling agents, and bioadhesives. The backbone of the transdermal drug delivery process is the polymer. These polymers used in transdermal drug delivery systems (TDDS) must exhibit good stability and consistency with the drug and other components of the system [7]. This is crucial to ensure the safe and successful release of the medication. The polymer acts as a cornerstone in controlling the release of the drug from the system, allowing for a more controlled and efficient delivery. By utilizing polymers, the frequency of dosing can be reduced, and the drug's efficacy can be improved by localizing its action at the desired site. Polymers used in TDDS can be derived from natural sources, semi-synthetic sources, or can be completely synthetic. Regardless of their origin, these polymers

are essential in the manufacturing of various dosage forms, including solid monolithic matrix systems, plates, films, beads, microparticles, nanoparticles, inhalable and injectable systems, as well as viscous liquid formulations [7]. Within these formulations, polymers serve multiple roles, such as binders, matrix formers, drug release regulators, film coating formers, thickeners, viscosity enhancers, stabilizers, disintegrates, solubilizers, emulsifiers, suspenders, gelling agents, and bioadhesives [8].

## 1. Advantages of Natural polymers

Polymers produced naturally by living organisms are therefore biodegradable and biocompatible.

Natural polymer has not any kind of toxic effects on human.
In fact, carbohydrates consisting of repeated units of monosaccharides. We are therefore non-toxic.

It is easily accessible and economic cost is low.

Safe and without side effects–they come from a natural source and are therefore safe and without side effects [9].

## 2. Disadvantages of Natural polymer

Microbial contamination–They are exposed to external environment during processing and microbial contamination is therefore likely to occur.

Variation from batch to batch–Synthetic manufacturing is managed with defined component amounts while the development of natural polymers depends on the environment and various physical factors.

Various Natural polymers used in Transdermal drug delivery system (TDDs) such as Gum Arabic/ Gum Acacia,Agar,Alginates,Xanthan Gum,Tamarind Gum, Moringa Oleifera Gum, Tragacanth, Chitosan, Locust Bean Gum, Jackfruit Mucilage

## 3. Pharmacokinetic model for percutaneous absorption

Figure 1 illustrates the process of how a drug molecule is distributed and diffused across different layers of the skin, eventually entering the systemic circulation. This model accurately assigns true physicochemical significance to the rate constants, which can be predicted based on fundamental physical properties [10]. In Figure 2, the events that occur during percutaneous absorption are depicted. These events are crucial in understanding the process of drug absorption through the skin [11]. The kinetic parameters associated with this process hold significant importance [12]. For instance, f(K1) represents the input kinetics from the transdermal device in a "membrane-controlled" system. It comprises both First-order (K1) and zero-order (K0) components. The former signifies the release of the drug from the contact adhesive, while the latter indicates the limited leaching of the drug from the reservoir through the membrane.

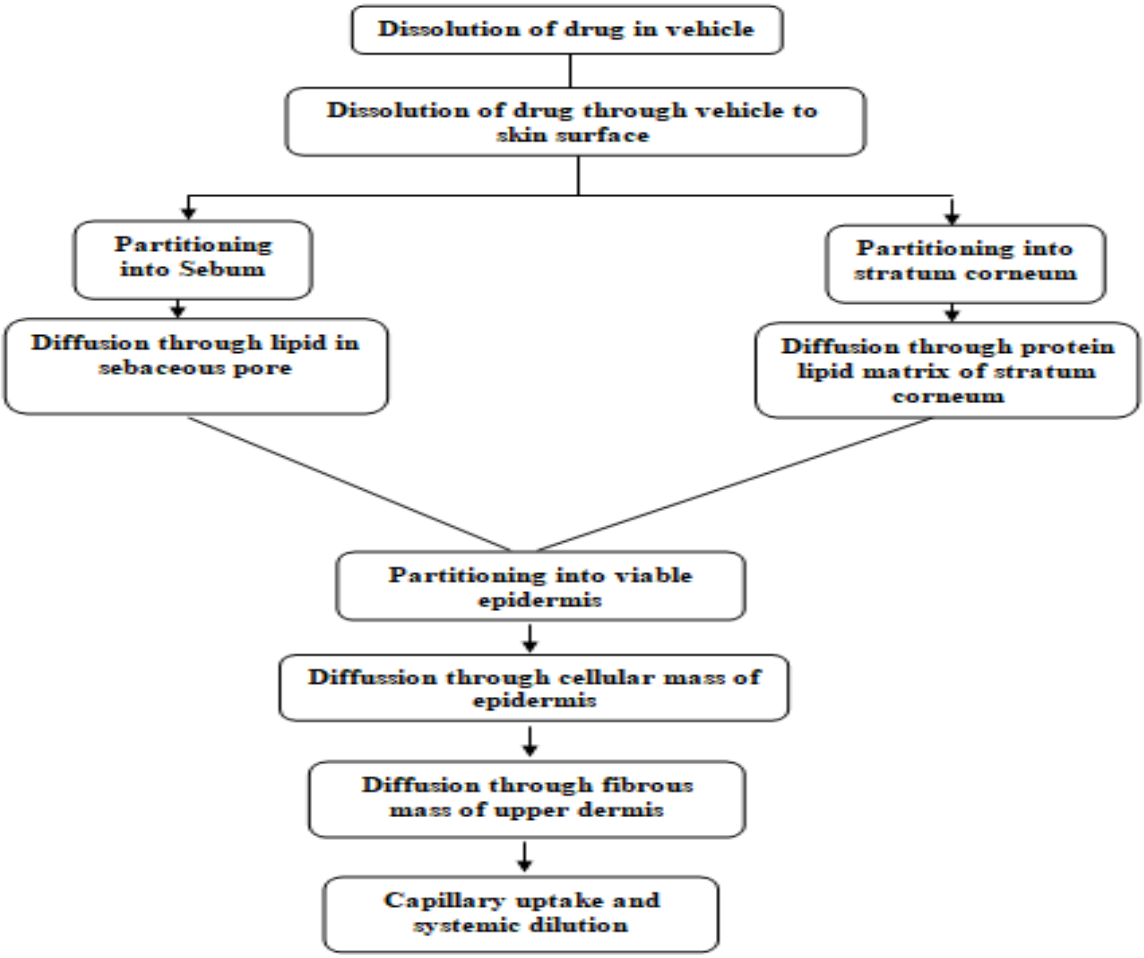


**Figure 1: Events governing percutaneous absorption**

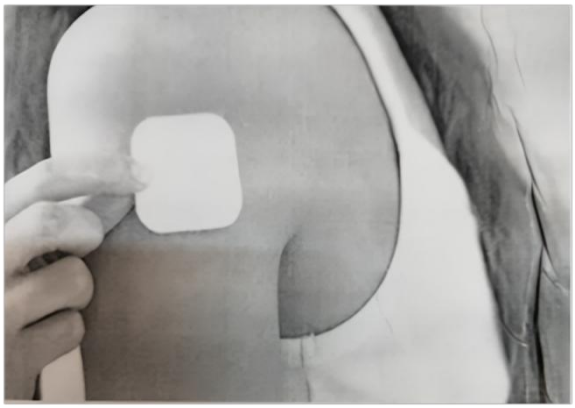

**Figure 2: A patch on skin.**

The competition for the drug between the patch and the stratum corneum is reflected by Kr, which will be small if the system is well designed (Figure 3). On the other hand, K1 and K2 are first-order rate constants that describe the transport of the drug across the stratum corneum and viable tissue, respectively. These constants are directly proportional to the diffusion coefficients through the layers of skin and can be simplified by relating them to the molecular weight (M) of the penetrant using an equation.

D=C.M1/3---------- (1)

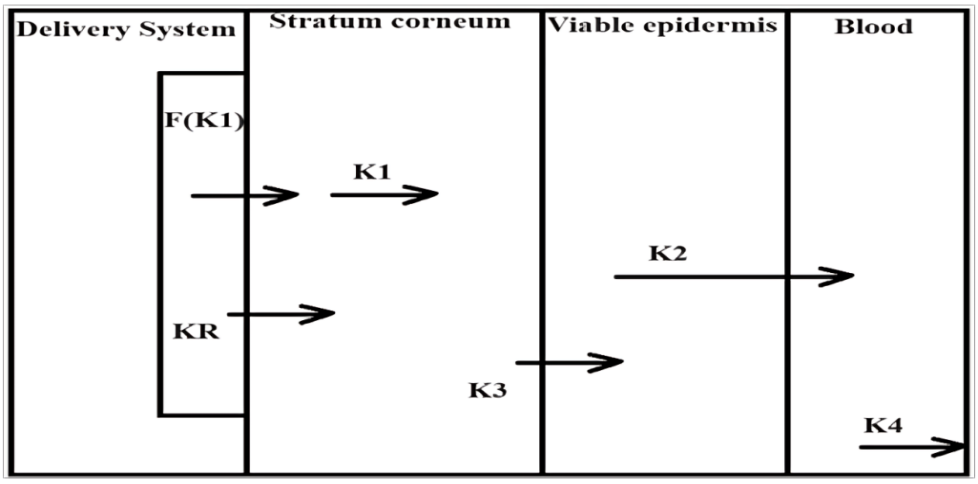


**Figure 3: Pharmacokinetic model for transdermal drug delivery system.**

**4. The factors influencing the suitability of a drug for TDDs are as follows:**

- Potency of the drug- The daily systemic dose should be s 20 mg.
- Molecular size- The drug should have a MW of <500 Daltons.
- Lipophilicity- The log P should be within the range of 1-3.
- Melting point- Should be < 2000C
- Hydrogen bonding groups should be ≤ 2.
- Irritation--The drug should not be directly irritant to the skin.
- Immunogenicity-The drug should not stimulate an immune reaction in the skin [13].

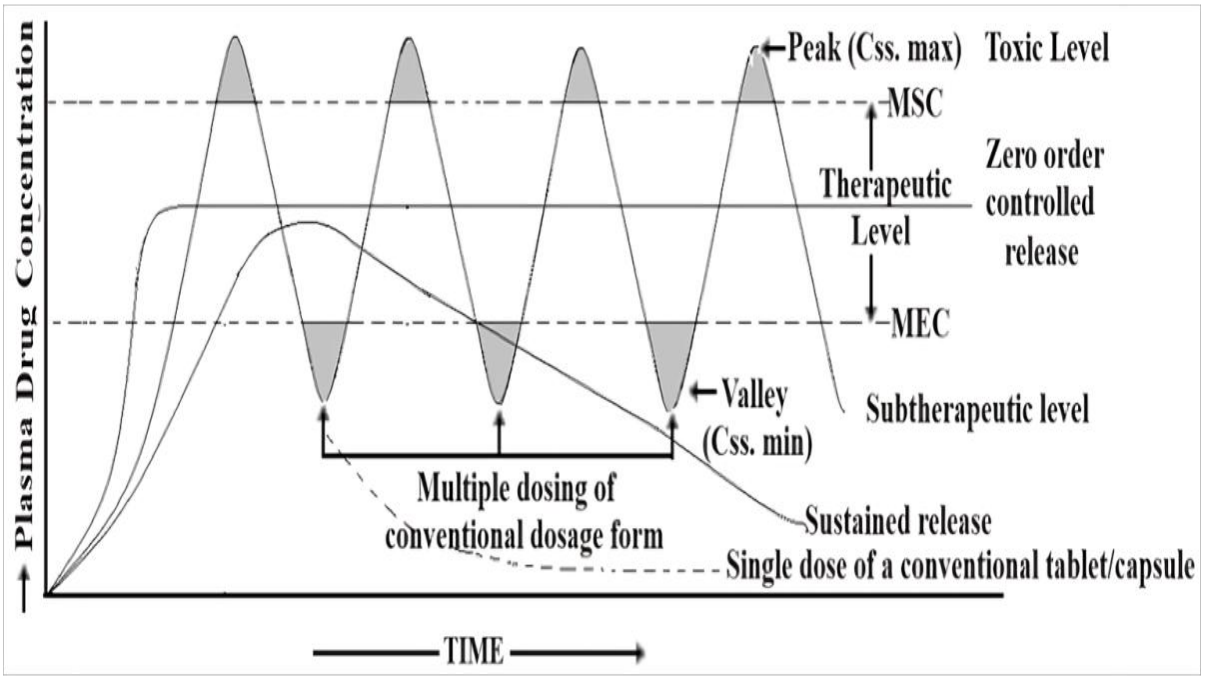


**Figure:1 A hypothetical plasma concentration-time profile of single dose conventional form in comparison to controlled release**

## IV.TRANSDERMAL DRUG DELIVERY SYSTEM

Transdermal drug delivery systems (TDDS) refer to self-contained and discrete dosage forms that are designed to deliver drugs to the systemic circulation at a controlled rate when applied to the intact skin. This method of drug delivery is particularly suitable for potent and low-molecular-weight therapeutic agents that cannot withstand the harsh environment of the gastrointestinal tract and are susceptible to significant first-pass metabolism by the liver. These transdermal drug delivery systems typically come in the form of patches that are applied topically to the skin. They are designed to release the drugs at a predetermined and controlled rate, allowing for systemic effects. These patches can be either active or passive in design, providing an alternative route for medication delivery. The mechanism of action for transdermal patches is relatively straightforward. The medication is incorporated into the patch at a relatively high dosage, and the patch is worn on the body for an extended period. Through a process of diffusion, the drug can enter the bloodstream directly through the skin. The high concentration of the drug in the patch ensures a continuous release into the bloodstream, maintaining a constant concentration of the drug in the blood flow over an extended period. Transdermal drug delivery systems offer several advantages over other routes of administration. They provide a non-invasive method of drug delivery, eliminating the need for injections or oral ingestion. This can be particularly beneficial for patients who have difficulty swallowing or who require long-term medication. Additionally, transdermal patches offer a controlled release of the drug, minimizing fluctuations in drug concentration and providing a more consistent therapeutic effect. In conclusion, transdermal drug delivery systems are an effective and convenient method of administering drugs that are unable to withstand the gastrointestinal tract or are subject to significant first-pass metabolism. These self-contained patches deliver drugs at a controlled rate through the intact skin, providing systemic effects and maintaining a constant concentration of the drug in the bloodstream [14].

### 5. Advantages of TDDS: This approach to the delivery of drugs offers many benefits over traditional methods

- To replace the oral route.
- Transdermal drug delivery allows gastrointestinal absorption to be prevented with the associated enzyme and pH-related deactivation pitfalls.
- This approach also makes it possible to minimize pharmacological dosage due to the shorter metabolization process of the transdermal route versus the gastrointestinal path way.
- The patch also allows for constant dosage rather than the medication level peaks and valleys associated with medications given orally. Multi-day single application therapy.
- Rapid confirmation of treatment in case of emergency and the ability to quickly avoid the effects of drugs by removing patches.
- Reduce side effects on the gastrointestinal tract.
- Interactions with the elimination of drug food.
- Improved patient adherence as follows
- Provisions of simplified therapeutic regimen.
- Painless delivery of drug.
- Eliminates swallowing.

- No chances of forgetting the dose once the device is applied to skin.
- Easy to carry a patch in the wallet or ladies' purse.
- Patches deliver less wear and tear-sensitive problems than tablets.
- TDDS prevents medication contact in GIT in a multi-drug regimen.
- Simply removing the drug delivery device from the skin surface makes it easy to terminate the drug.
- Without any aid, the TDDS system can be used, making it the most suitable formulation; tablets and capsules, for example, need little water. Liquid oral preparation needs a teaspoon and parenting needs a specialized person, whereas if a patient is told to apply TDDS patch, he/she can do it anywhere, e.g. in the office, theatre, club, or household, without any help.
- Compared to other forms of dosage, the chance of toxicity due to additives such as xiv. preservatives, stabilizing antioxidants, etc.
- xv. The dose dumping problem is least present in TDDS, since the stratum corneum is more resistant than the inner membranes (i.e. mucous membrane in orally controlled release delivery systems) and the stratum corneum itself is a rate-limiting factor.
- xvi. Need not be sterile, it avoids the problem of storage [15,16,17,18].

### 6. Disadvantages of TDDS

- The medicine that requires high blood levels cannot be given and can even cause skin irritation or sensitization.
- It may not adhere well to all skin types and may be uncomfortable to wear.
- High product costs are also a major drawback to this product's wide acceptance.
- Properties that influence the vehicle's transdermal delivery of the medicine.
- Activation of the pharmacological response through the skin barrier.

Drugs that can be administered orally once a day, with reproducible bioavailability, and that are well tolerated by patients do not need to be patched. Drugs must not be locally irritating or sensitizing as their regulatory approval is most likely prevented by the provocation of significant skin reactions under a transdermal delivery system [19].

## V. FACTORS AFFECTING TDDS

### 1. Partition Coefficient

Molecules with a moderate partition coefficient and those that are highly lipophilic tend to take the intercellular route when crossing the stratum corneum. This pathway allows these molecules to separate the aqueous viable epidermal tissues from the stratum corneum. On the other hand, more hydrophilic molecules are more likely to use the transcellular route.To achieve optimal transdermal permeability, a water partition coefficient of 1 or higher is typically necessary. It is worth noting that the water partition coefficient can be modified without impacting the pharmacological activity of the drug [20].

## 2. Molecular Size

The flux of a material through human skin is influenced by the size of the molecule. The relationship between transdermal flux and molecular weight is inversely proportional to the molecular size. In transdermal delivery, drugs with a molecular weight within the range of 100-500 are commonly used.

## 3. Solubility/Melting Point

Under typical conditions of temperature and pressure, organic substances with elevated melting points generally exhibit poor solubility in water. Lipophilic compounds have a tendency to penetrate the skin more rapidly compared to hydrophilic ones. The characteristic of being lipophilic is advantageous for substances intended for transdermal delivery, and the molecule must possess some level of solubility in water since topical medications are commonly administered in an aqueous form [21].

## 4. Ionization

Through the lipid barrier, a unionized type drug can permeate more than ionized drugs.

## 5. Other Factors

The interactions between a drug substance and tissue can encompass a wide range of forces, from hydrogen bonding to weak Vander Waals forces. The impact of drug binding on tissue flux can differ based on the specific permeate being considered. Depending on the type of formulation chosen, certain interactions may be crucial in a transdermal delivery system. These interactions play a significant role in determining the effectiveness and efficiency of drug delivery through the skin barrier (Vinod K, et, al.,2010).

- **Physiological Factors:** Skin barrier property in the neonate and young infant: The delicate nature of newborn skin makes it more prone to irritation from various factors, including the pH levels and hydration of the stratum corneum. These variables can further exacerbate the susceptibility of newborn skin to irritants, as evidenced by the significantly higher surface pH values found in newborn skin compared to adult skin. Additionally, newborn skin undergoes changes in metabolic capacity that are not fully developed until later stages of infancy, around 2 months to 6-12 months of age. These developmental changes may contribute to the heightened sensitivity of newborn skin to irritants, making it more susceptible than older infants' skin.Furthermore, newborn skin is characterized by being slightly hydrophobic, meaning it repels water, and tends to be relatively dry and rough in texture. These unique characteristics of newborn skin also play a role in its increased vulnerability to irritants, highlighting the importance of gentle care and attention when it comes to newborn skincare.

  Skin barrier properties in aged skin: In comparison to other types of skin, the aged skin does not exhibit any significant anatomical changes. However, there is an observed increase in the surface area of the corneocyte region, which could potentially impact the function of the stratum corneum. This increase in surface area leads to a reduction in the amount of interneomeoctye space per unit volume of the

stratum corneum. Additionally, as individuals age, the moisture content of their skin tends to decrease. Furthermore, the dermo epidermal junction becomes flattened, and there is an expansion in the region that is available for dermis diffusion [22].

- **Race:** The skin exhibits notable variances in anatomical and physiological functions between individuals with black and white skin. Research indicates that black skin tends to have higher intracellular cohesion, lower lipid content, and elevated levels of electrical skin resistance in comparison to white skin. These differences suggest that the stratum corneum in black skin may play a role in regulating radical irritant responses more effectively. The increased intracellular cohesion in black skin could contribute to a more robust barrier function, potentially offering better protection against environmental aggressors. Meanwhile, the lower lipid content in black skin may affect its hydration levels and overall skin health differently than in white skin. Additionally, the higher electrical skin resistance observed in black skin could indicate variances in skin sensitivity and reactivity to external stimuli. Understanding these distinct characteristics of black and white skin is crucial for developing tailored skincare products and treatments that cater to diverse skin needs. By acknowledging and studying these differences, skincare professionals can better address concerns related to skin health, aging, and conditions that may affect individuals with different skin types. Ultimately, this knowledge can lead to more effective and inclusive skincare practices in the beauty and medical industries.

- **Body:** The permeability of different skin sites is not solely determined by the thickness of the stratum corneum, as different substances show different levels of permeability across various skin sites. The genital tissue is often the most permeable site for delivering drugs through the skin. Similarly, the skin on the head and neck, like the arms and legs, is also relatively permeable.

- **Other Physiological Factors:** There are a variety of conditions that can result in eruptions on the surface of the skin. In such instances, the protective barrier properties of the stratum corneum become compromised, enabling medications to penetrate through and reach the skin. Skin conditions that are linked to a weakened skin barrier function often involve a significant loss of water through the skin during active disease, sometimes reaching levels up to 20 times higher than normal. This heightened loss of water contributes to the overall severity of the condition. The diminished barrier function, which is often accompanied by visible scaling of the skin, facilitates greater absorption of externally applied substances through the skin. The absence of intercellular lipids in the affected areas reduces the natural lipid pathway within the skin, leading to an increased permeability of the skin barrier. (Vinod K, et, al.,2010).

- **Environmental Factors**
  - **Sunlight:** Sun exposure can lead to a thinning of the walls of blood vessels, which in turn can cause bruising even with minor trauma in the sun-exposed areas. Additionally, one of the most prominent effects of sun-induced pigmentation changes is the development of freckles or solar lentigines, which are dark spots on the skin[23].

- **Cold Season:** The cold season often leads to the uncomfortable condition of itchy and dry skin. In response to the drying effects of the weather, the skin naturally produces more oil. To alleviate the symptoms of dry skin, using a high-quality moisturizer is recommended. Additionally, maintaining proper hydration by drinking plenty of water can contribute to a radiant and well-hydrated complexion.
- **Air Pollution:** The presence of air pollution has the potential to clog pores and promote the growth of bacteria on the skin's surface, ultimately resulting in the development of acne or blemishes that can hinder the skin's ability to absorb medications topically.Additionally, unseen chemical pollutants in the atmosphere have the ability to disrupt the skin's natural defense mechanisms, causing a breakdown in the skin's essential oils that typically help maintain moisture levels and promote a smooth complexion[24].

## VI.TYPES OF TRANSDERMAL PATCHES

Developed and manufactured various types of transdermal systems. The TDDS types, for example:

### 1. Matrix diffusion-controlled systems

Drug reservoirs in these methods are created through the uniform distribution of drug particles within a hydrophilic or lipophilic polymer matrix, as illustrated in Figure 4. This distribution process can be achieved by mixing finely ground drug particles with a liquid polymer or a highly viscous base polymer, then cross-linking the polymer chains. Alternatively, drug solids can be blended uniformly with a rubbery polymer at a high temperature to form the reservoir [25].

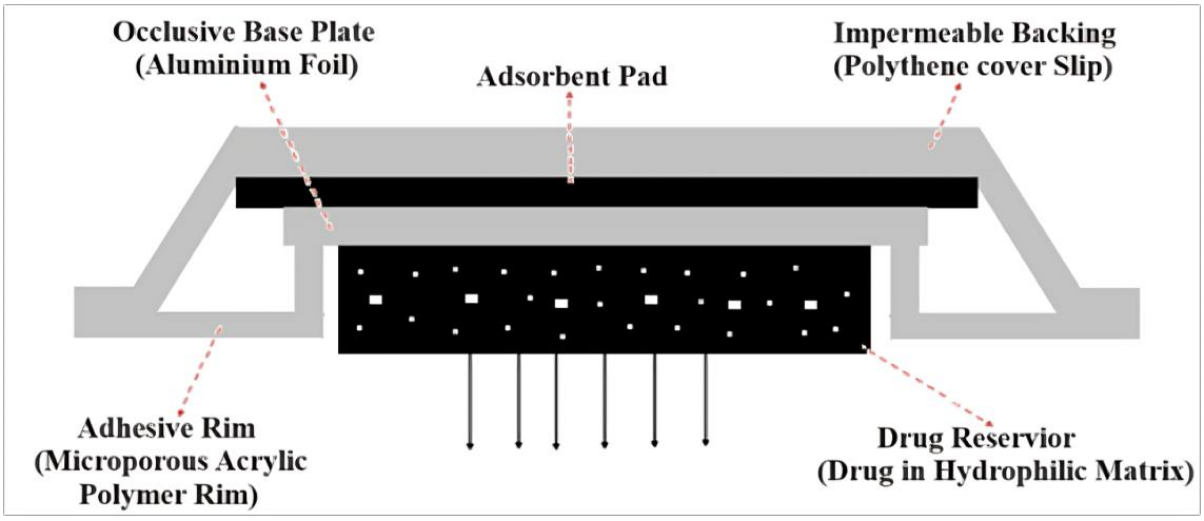


**Figure 4: Matrix diffusion-controlled systems.**

The rate of drug release from this type of system is defined as

$$dQ/dt = [ACp.\ Dp/2t]1/2 \text{---------- (2)}$$

Where A is the intitial drug loading dose dispersed in the polymer matrix and Co and Dy are the solubility and diffusivity of the drug in the polymer respectively. Since, only the drug

species dissolved in the polymer can release, Cp is essentially equal to Cg where Cg is the drug concentration in the reservoir component.

A Q versus ta drug release profile is obtained at steady state and is defined by

Q/t1/2 =[(2A-Cp) Cp Dp]1/2---------- (3)

The advantage of the matrix dispersion-type transdermal system is the absence of dose dumping since the polymer cannot rupture [25].

**2. Membrane Permeation-controlled Systems**

Within this particular system design, the drug reservoir is fully enclosed within a flat compartment made from a drug-impermeable material such as metallic plastic laminate. This compartment also includes a rate-controlling polymeric membrane, which can either be microporous or non-porous, like ethylene vinyl acetate (EVA) copolymer, with a specific drug permeability characteristic [27]. Additionally, a thin layer of hypoallergenic adhesive polymer that is compatible with the drug, such as silicone or polyacrylate adhesive, may be applied onto the outer surface of the rate-controlling membrane. This layer serves the purpose of ensuring close contact between the transdermal system and the skin surface, enhancing the effectiveness of drug delivery through the skin.

Synthetic Elastomers: Polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.

Synthetic Polymers: Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinyl pyrrolidone, Polymethyl methacrylate, Epoxy etc.

**Drug:** The drug should be chosen with great care in order to successfully establish a transdermal drug delivery system. Some of a drug's desirable properties for transdermal delivery are as follows: Physicochemical properties

- The drug should have a molecular weight of less than approximately 1000 Daltons.
- The drug should have an affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
- The drug should have a low melting point.
- Along with these properties, the drug should be potent, have a short half-life and be non-irritating [36].

Permeation enhancers are substances that can increase the permeability of the skin by modifying its barrier properties to allow for the desired substance to penetrate through. These enhancers can be categorized into different groups based on their mechanisms of action.

Solvents, like methanol, ethanol, dimethyl sulfoxide, dimethyl acetamide, and dimethyl formamide, are compounds that can enhance penetration by either creating a pathway for the substance or by fluidizing the lipids in the skin.

Surfactants, on the other hand, are compounds that can improve the transport of polar substances, especially hydrophilic drugs, through the skin. The effectiveness of a surfactant in enhancing penetration depends on the structure of its polar head group and the length of its hydrocarbon chain, also called an ionic surfactant. Examples of surfactants include dioctylsulphosuccinate, sodium lauryl sulfate, and decodecylmethyl sulphoxide.

Nonionic surfactants, such as Pluronic F127 and Pluronic F68, are also known to enhance permeation.

Bile salts, such as sodium MS taurocholate, sodium deoxycholate, and sodium tauroglycocholate, can also act as permeation enhancers.

Binary systems, like propylene glycol-oleic acid and 1, 4-butane diol linoleic acid, are believed to open up both the heterogeneous multi-laminate pathway and the continuous pathways in the skin, thereby enhancing permeation.

Lastly, pressure-sensitive adhesives, such as polyacrylates, polyisobutylene, and silicon-based adhesives, are used to maintain intimate contact between the transdermal system and the skin surface. These adhesives adhere to finger pressure and exert a strong holding force, but can be easily removed from smooth surfaces without leaving a residue [37].

Backing laminates: Elastic backing membranes play a crucial role in maintaining a strong connection with the drug reservoir, ensuring that the drug remains within the dosage form and does not escape through the edges. Additionally, these membranes enable printing on the surface. They are impermeable materials that protect the item when applied to the skin. Examples of such backing membranes include metallic plastic laminate, plastic backing combined with an absorbent pad and an occlusive base plate made of aluminum foil, as well as adhesive foam pads made of flexible polyurethane with an occlusive base plate [38].

**Release liner:**

- A release liner is a film covered with an anti-adherent coating.
- It is removed and discarded before the application of the patch to the skin.
- It is regarded as a part of the primary packaging material.

However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer, and water.

Typically, release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a coating layer made up of silicon or Teflon.

**Other examples include polyester foil and metalized laminates [39].**

Other excipients: Various solvents such as chloroform, methanol, acetone, isopropanol, and, dichloromethane are used to prepare drug reservoirs. In addition, plasticizers such as di-butylphthalide, triethyl citrate, polyethylene glycol, and propylene glycol are added to provide plasticity to the transdermal patch [40].

## VII. PATHWAY OF TRANSDERMAL PERMEATION

Drug permeation through the skin involves two main pathways: spreading through the intact epidermis and passing through the appendages of the skin, such as hair follicles and sweat glands. These appendages create shunt pathways that bypass the intact epidermis. However, it is important to note that these skin appendages only cover approximately 0.1 percent of the total human skin surface. Therefore, their contribution to drug permeation is generally considered to be minimal, with only a few exceptions. The primary barrier to drug permeation through the skin is the Stratum corneum, which typically limits the passage of drugs [41]. There are two identified pathways through the intact barrier: the intercellular lipid route between the corneocytes and the transcellular route crossing through the corneocytes and the intervening lipids. In both cases, diffusion through the intercellular lipid matrix is necessary and is recognized as the major determinant of the rate of drug transport through the skin [42].

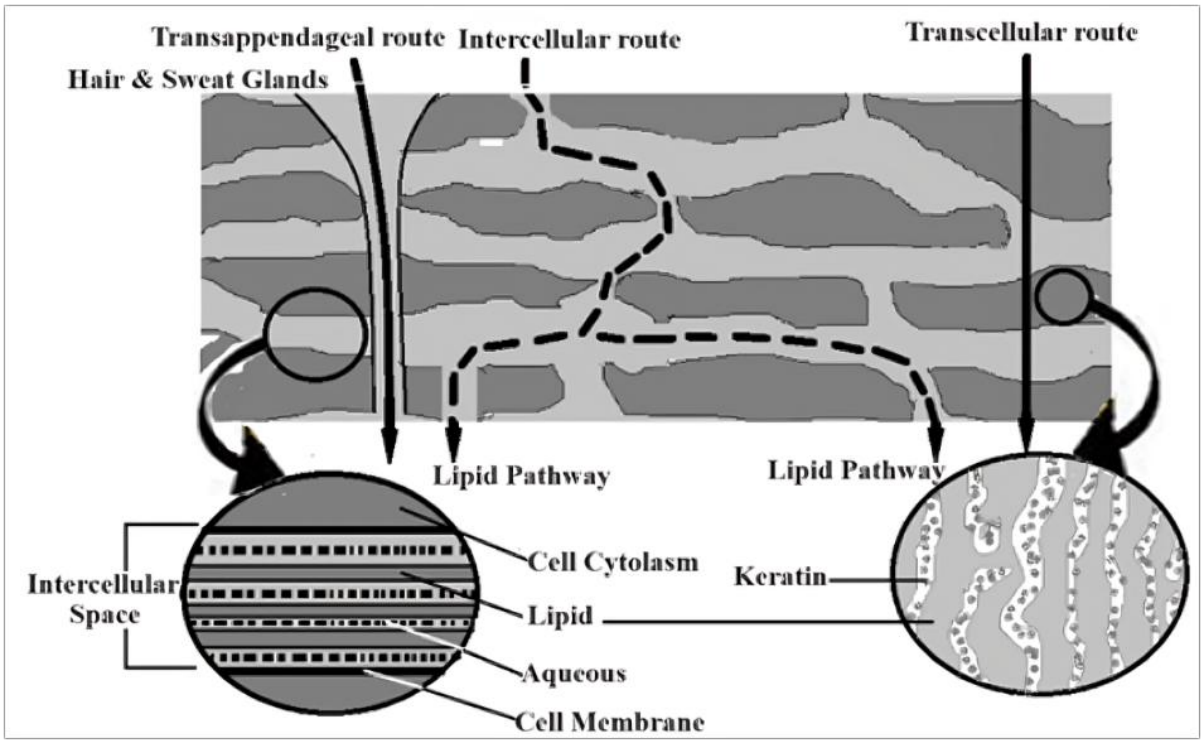


**Figure 5: Drug pathway through skin.**

### 3. Kinetics of Transdermal Permeation

Knowledge of kinetics of skin permeation is essential for the successful design of transdermal therapy systems. The following steps are involved in the transdermal permeation of a drug:

### 4. Sorption By Stratum Corneum

- Penetration of drug through epidermis.
- Uptake of the drug by the capillary network in the dermal papillary layer [43].

This permeation can be possible only if the drug possesses certain physiochemical properties. The rate of permeation across the skin is given by

$dQ/dt = Ps (Cd – Cr)$ ---------- (4)

Where, Cd and Cr are the concentration of the skin penetrant in the donor compartment i.e. on the surface of stratum corneum and in the receptor compartment i.e. body respectively. Ps is the overall permeability coefficient of the skin tissue to the penetrant [44]. This permeability coefficient is given by the relationship-

$Ps = DssKs/hs$----------(5)

Where Ks is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system onto the stratum corneum [45], Dss is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues and hs is the overall thickness of skin tissues. As Ks, Dss, and hs are constant under given conditions the permeability coefficient Ps for a skin penetrant can be considered to be constant [46]. From the equation, it is clear that a constant rate of drug permeation can be obtained only when Cd >> Cr i.e. the drug concentration at the surface of the stratum corneum Cd is consistently and substantially greater than the drug concentration in the body Cr [47]. The equation becomes

$dQ/dt = PsCd$---------- (6)

The rate of skin permeation is constant provided the magnitude of Cd remains fairly constant throughout the course of skin permeation. For keeping Cd constant, the drug should be diffusion from the device at a rate Rr i.e. either constant or greater than the rate of skin uptake Ra i.e. Rr>> Ra. Since Rr>> Ra, the drug concentration on the skin surface Cd is maintained at a level equal to or greater than the equilibrium solubility of the drug in the stratum corneum Cs.i.e. Cd>>Cs [48]. Therefore, a maximum rate of skin permeation is obtained and is given by the equation:

$(dQ/dt)\ m = PsCs$---------- (7)

## VIII. APPROVED PRODUCTS

Currently, ClinicalTrials.gov lists over 900 trials that include the word ‘transdermal’ in their description (search conducted December 2019 [48]. Unfortunately, there are a large number of trials with the same four drugs (nicotine, oestradiol, fentanyl, and testosterone), and the fact that most of the trials relate to only a few drugs is no surprise given the exclusive nature of marketed transdermal drugs, the selective nature of the skin as a barrier to diffusion and the physicochemical and pharmacokinetic properties of marketed transdermal drugs [48]. Furthermore, many of the case studies relate to chronic pain conditions and nausea, or studies involving several drugs with comparisons to other delivery routes such as lozenges or injections compared to patches. Table 1 lists some transdermal drugs for systemic delivery that have been launched in the USA and EU. These tables further emphasize what makes a successfully marketed passive transdermal candidate and where the limitations li

**Table 1. Some Transdermal drugs for systemic delivery launched in the USA and EU**

| Year | Drug | Indication | Product Name | Company Name |
|---|---|---|---|---|
| 1979 | Scopolamine | Motion Sickness | Transderm-Scop | Novartis Consumer Health (Parsippany, NJ) |
| 1986 | Estradiol | Menopausal Symptom | Estraderm | Novas (East Hannover, NJ) |
| 1990 | Fentanyl | Chronic pain | Duragesic | Janssen Pharmaceutica (Titusville, NJ) |
| 1995 | Lidocaine/epinephrine | Local dermal analgesia | Iontocaine | Iomed (Salt Lake City, UT) |
| 1998 | Estradiol/norethidrone | Menopausal Symptoms | Combipatch | Novartis (East Hannover, NJ) |
| 1999 | Lidocaine | Post-herpetic neuralgia pain | Lidoderm | Endo Pharmaceuticals (Chadds Ford, PA) |
| 2001 | Ethinyl estradiol/Norelgestromin | Contraception | Ortho Evra | Ortho-McNeil Pharmaceutical (Raritan, NJ) |
| 2003 | Estradiol/Levonorgestrel | Menopausal symptoms | Climara Pro | Bayer Healthcare Pharmaceuticals(Wayne, NJ) |
| 2003 | Oxybutynin | Overactive bladder | Oxytrol | ---------- |
| 2004 | Lidocaine/(ultrasound) | Local dermal analgesia | SonoPrep | Echo Therapeutics (Franklin, MA) |
| 2005 | Lidocaine/tetracaine | Local dermal analgesia | Synera | Endo Pharmaceuticals (Chadds Ford, PA) |
| 2006 | Fentanyl HCL(iontophoresis) | Acute postoperative pain | Ionsys | Alza, Mountain View, CA |
| 2006 | Selegiline | Major depressive disorder | Emsam | Bristol-Myers Squibb (Princeton,NJ) |
| 2007 | Rotigotine | Parkinson's disease | Neupro | Schwarz Pharma (Mequon,WI) |
| 2007 | Rivastigmine | Dementia | Exelon | Novartis (East Hannover,NJ) |
| 2008 | Methyl Salicylate | Muscle and joint pain | Salonpas | Hisamitsu Pharmaceutical |
| 2009 | Capsaicin | Neuropathic pain | Qutenza | NeurogesX |
| 2010 | Buprenorphine | Chronic pain | Butrans | Purdue Pharma |

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