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Transdermal Drug Delivery Systems with Special Emphasis on its Components, Evaluation Methods and Recent Advancements

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ABSTRACT
Transdermal Drug Delivery Systems (TDDS) have revolutionized modern medicine by offering non-invasive administration methods that enhance patient compliance and minimize adverse effects. This article delves into the fundamental components of TDDS, namely the drug, the polymer matrix, and various excipients including penetration enhancers and backing layers, each of which plays a crucial role in ensuring effective drug release, adhesion to skin, and controlled permeation. The article further highlights recent advancements in this field, providing an in-depth analysis of innovative technologies such as microneedles, nanocarriers, hydrogels, and wearable devices, which are rapidly evolving to enhance drug permeability and delivery efficiency. A distinct focus is given to the development of bioresponsive transdermal systems, a ground-breaking approach offering individualized drug delivery based on specific patient's physiological conditions. Additionally, techniques like iontophoresis, electroporation, and heat-assisted methods are explored for their potential to facilitate drug passage through the skin. The review concludes by underscoring the future prospects of TDDS, with particular emphasis on potential applications in biosensing and vaccine delivery. Through this comprehensive exploration, the article provides a holistic understanding of the transdermal drug delivery landscape, its key components, current innovations, and future directions.

Keywords - Transdermal Drug Delivery Systems (TDDS), Microneedles, Bioresponsive Systems, Nanocarriers, Iontophoresis.

I. INTRODUCTION

Rapid advancements in the field of drug delivery have been observed in recent years, exceeding the pace of development witnessed over the past two decades. Enhanced patient compliance and optimized therapeutic effectiveness are integral features of these contemporary drug delivery systems.

In the quest for innovative therapeutic interfaces, the human skin has been recognized as a potential gateway for systemic drug administration. This concept has led to the development of the Transdermal Drug Delivery System (TDDS). TDDS, a subset of controlled drug delivery mechanisms, is specifically designed to facilitate the penetration of drugs through the skin at a predetermined and controlled rate. TDDS consists of adhesive devices that contain specific drugs, designed to administer a defined amount of medication to the intact skin at a pre-set rate, which then enters the systemic circulation.(Anantrao et al., 2021)

Transdermal drug administration confers considerable advantages over injectable and oral routes, the most significant being improved patient adherence and circumvention of first-pass metabolism, respectively. In terms of innovative research within the drug delivery sphere, transdermal delivery is vying for the leading position with oral administration.

Figure 01: Transdermal Patches

Oral administration is typically characterized by achieving and maintaining therapeutic drug concentration within the body via regular administration of fixed doses. However, this approach results in a peak-and-trough profile of drug concentration in the body, increasing the risk of adverse effects or therapeutic failure. Furthermore, substantial drug quantity might not reach the target organ and constant monitoring is required to prevent overdosing.[2](Parmar & Bansal, 2021)

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In contrast, the transdermal route can mitigate these limitations associated with oral administration. It also allows for the replication of the benefits of intravenous drug infusion, such as bypassing first-pass hepatic elimination, to maintain constant and therapeutically effective drug levels in the body. All of these benefits can be achieved without the potential hazards associated with intravenous infusion.

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEMS (TDDS)

Transdermal drug delivery systems (TDDS) offer a variety of advantages, which make them an appealing alternative to conventional delivery methods like oral administration and hypodermic injections (Prausnitz& Langer, 2008; F.-Y. Wang et al., 2021; M. Wang et al., 2016)

1. **Non-Invasive**: TDDS is a non-invasive method of delivering drugs, making it more comfortable for patients and reducing the risk of complications associated with injections, such as infections or pain.
2. **Bypasses First-Pass Metabolism**: Transdermal delivery allows drugs to bypass the gastrointestinal tract and first-pass metabolism in the liver. This can enhance the bioavailability of certain drugs, and prevent potential side effects related to the digestive system.
3. **Sustained Drug Delivery**: TDDS can maintain an effective rate of drug delivery over time. This ensures a steady rate of circulation, leading to more predictable and controlled therapeutic effects.
4. **Patient Compliance**: Given their convenience, transdermal patches can enhance patient compliance. They can be applied easily, are non-disruptive to daily activities, and only need to be replaced occasionally.
5. **Wide Range of Applications**: With more than 19 drugs or drug combinations currently administered using FDA-approved transdermal delivery systems, TDDS can be employed for a wide range of medications.
6. **Termination at Any Time**: Transdermal drug delivery can be stopped at any time by simply removing the patch, giving patients and healthcare providers control over treatment.
7. **Improved Skin Barrier Penetration**: Emerging developments, such as microneedles, have facilitated improved skin barrier penetration for the delivery of drugs, making TDDS even more efficient.

DISADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEMS (TDDS):

While transdermal drug delivery systems (TDDS) offer numerous advantages, they also come with several drawbacks:(Escobar-Chavez et al., 2012; Peña-Juárez et al., 2022; Prausnitz et al., 2004; Prausnitz& Langer, 2008)

1. **Skin Irritation**: The drug, adhesive, or excipients in the patch formulation may cause skin issues such as rashes, local irritation, erythema, or contact dermatitis. This could cause discomfort for the patient and might limit the use of transdermal patches.
2. **Limited Drug Selection**: Only drugs with a certain set of physicochemical properties (like being lipophilic) can effectively penetrate the skin and reach systemic circulation. Drugs with a hydrophilic structure generally have a harder time crossing the skin barrier, limiting the types of drugs that can be delivered transdermally.
3. **Variable Absorption Rates**: Skin type, location, and condition can impact the rate of drug absorption, potentially leading to inconsistencies in drug delivery.
4. **Limited Drug Dosage**: Transdermal patches are typically more suitable for delivering small, lipophilic, low-dose drugs. The delivery of larger molecules, such as proteins, can be challenging and may require specialized methods or devices to enhance their passage through the skin.
5. **Potential for Overdosing**: If a patch is damaged or if multiple patches are applied, there could be a risk of overdosing.

These limitations necessitate careful consideration of the drug, patient, and intended use before deciding to utilize a transdermal drug delivery system.

Skin and drug penetration:

The primary aim of a transdermal drug delivery system (TDDS) is to administer systemic medication via topical application on unbroken skin. It is thus crucial to understand the structural and biochemical attributes of human skin, as well as those characteristics that influence its barrier function and drug permeation rate.

The skin, one of the body's largest organs, is anatomically divided into two key layers: the epidermis and dermis (or corium), both of which

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are interspersed with hair shafts and gland ducts. The skin of an average adult spans approximately 2 m^2. The main layers of the skin, from the inside out, include the fatty subcutaneous layer (hypodermis), the connective tissue of the dermis, and the stratified avascular cellular epidermis. This multilayered organ accounts for roughly one-third of the total blood circulation in the body. (Waghule et al., 2019)

The epidermis, which is about 150-µm thick, stems from an active basal cell population and sits as the skin's outermost layer. The differentiation process prompts cell migration from the basal layer to the skin surface. As the epidermis lacks blood vessels, nutrients and waste products must diffuse through the dermal-epidermal junction for vitality. The epidermis comprises five layers, listed from inside to outside: stratum germinativum (basal layer), stratum spinosum (spinous layer), stratum granulosum (granular layer), stratum lucidum, and stratum corneum (SC). Given that SC cells are lifeless, the epidermis without the SC is typically referred to as the viable epidermis.(Hadgraft, 1999)

The SC, containing 15-20 layers of keratin-filled corneocytes (fully differentiated keratinocytes) embedded in a lipophilic matrix, is viewed as the rate-limiting barrier for most molecular transdermal permeation. The unique extracellular matrix lipids constitute the only continuous phase from the skin surface to the SC base, are distinctively composed (ceramides, free fatty acids, and cholesterol), exist as multilamellar sheets despite lacking phospholipids, and form highly ordered, interdigitated configuration with gel phase membrane domains due to their predominantly saturated, long-chain hydrocarbon tails. When dry, the SC measures 10-15 µm in thickness, swelling up to 40 µm when hydrated. It is often portrayed as a "bricks and mortar" structure with keratin-rich corneocytes (bricks) set within an intercellular lipid-rich matrix (mortar).(Rim et al., 2008)

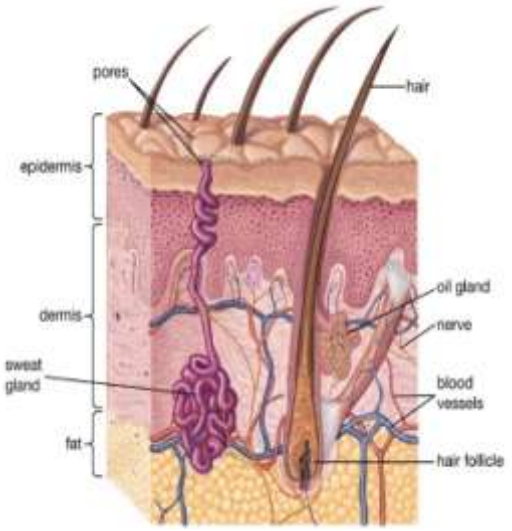

Figure 02: Anatomy of skin

Beneath the epidermis lies the dermis, a sturdy connective tissue layer of mesodermal origin that provides a foundation for the epidermis. The dermis, teeming with collagen fiber bundles and elastic tissue at superficial levels, comprises an intricate network of connective tissue. It houses fine blood vessels, lymphatics, nerves, hair follicles, sweat glands, and sebaceous glands.(Thomsett, 1986)

ROUTES OF PENETRATION

The pathways through which a drug molecule can traverse the intact Stratum Corneum (SC) are threefold: the appendageal, transcellular, and intercellular routes. The specific physicochemical properties of the molecule dictate the drug's permeation flux via these different routes.(Thotakura et al., 2017)

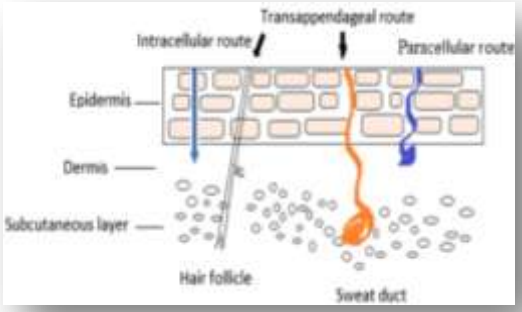

Figure 03: Routes of Penetration

The Appendageal Route, also known as shunt routes, permits drug penetration through the skin's

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appendages, specifically sweat glands and hair follicles along with their linked sebaceous glands. These appendages present a direct channel across the SC barrier. Recent research contradicts the longstanding assumption that follicles constitute roughly 0.1% of human skin's surface area. A study by Otberg and colleagues demonstrated that the count, opening diameter, and volume of follicles are key factors for drug delivery through these pathways. They found that follicular infundibula, particularly on the forehead, provides 13.7 mm^2/cm^2 of surface area, translating to about 13.7% of the forehead's surface area. Interestingly, the same study reaffirmed the traditional understanding that follicles constitute about 0.1% of the SC for forearm skin.(Konrádsdóttir et al., 2009)

The Transcellular Route involves drug penetration through corneocytes. These cells, loaded with highly hydrated keratin, offer an aqueous milieu conducive for the passage of hydrophilic drugs. The transcellular pathway not only necessitates the drug's partition into and diffusion through the keratin structures but also its penetration across the intercellular lipids.(Lee et al., 2008)

Lastly, **the Intercellular Route** comprises the diffusion of drugs through the continuous lipid matrix. This pathway poses two major challenges. First, considering the 'bricks and mortar' model of SC, the interdigitating arrangement of the corneocytes results in a winding path for intercellular drug permeation, contrasting with the more straightforward transcellular route. Second, the intercellular domain is characterized by alternating structured bilayers. Therefore, a drug must continuously partition into and diffuse through various aqueous and lipid domains. This route is widely regarded as the primary pathway for small, uncharged molecules to penetrate the skin.(Loan Honeywell-Nguyen et al., 2006)

Justification for the Use of Transdermal Drug Delivery Systems

Given the formidable barrier that the skin presents to molecular transport, the justification for a transdermal delivery approach needs to be carefully delineated. It's evident that there are circumstances where the most conventional method of drug administration – the oral route – isn't viable, necessitating the exploration of alternative routes.

While intravenous delivery of the medication bypasses numerous obstacles, such as gastrointestinal and hepatic metabolism, its invasive nature and associated patient apprehension (especially in cases of chronic administration) have motivated the pursuit of alternate strategies. Practically all anatomical orifices have been examined for their potential as optional drug delivery pathways. Despite this, transdermal delivery confers several unique benefits: The skin provides a relatively large and easily accessible surface area (1-2 m^2) for absorption, and the placement of a patch-like apparatus on the skin surface constitutes a non-invasive procedure, thus enhancing patient compliance, while permitting continuous intervention, including system repositioning, removal or replacement.(Zeb et al., 2019)

The evolution of Transdermal Drug Delivery Systems (TDDSs) over recent years has yielded numerous additional advantages. Among these are the capabilities for sustained release, which is particularly valuable for drugs possessing short biological half-lives and consequently necessitating frequent oral or parenteral administration, and for controlled input kinetics, vital for drugs with narrow therapeutic windows. Nonetheless, the deployment of transdermal drug delivery technology must be therapeutically warranted. For example, drugs with high oral bioavailability and those with infrequent dosing schedules, which are well-tolerated by patients, do not necessarily require such methodologies. Furthermore, transdermal administration is not designed to achieve immediate, bolus-type drug delivery; instead, it is typically geared towards slow, prolonged drug release over extended durations. As a result, drugs that induce tolerance or those, such as hormones, necessitating chronopharmacological control, are not suitable for this method, at least at present.(Huang et al., 2019)

Despite these limitations, a substantial range of drugs exists for which transdermal delivery would be beneficial, yet is currently impractical. This challenge essentially hinges on the nature of the stratum corneum (SC). The significant diffusional resistance presented by this membrane results in the feasible daily dose of a drug, which can be systematically delivered via a manageable patch-sized area, being confined to the 10 mg range. This restriction forms the first criterion for a successful transdermal candidate: the drug must be highly pharmacologically potent, with

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the requirement of therapeutic blood concentrations within the ng/ml range, or lower.

The second criterion stems from the selectivity of the SC concerning the type of molecule it permits for transportation across its barrier. Consequently, not all molecules that pass the 'potency' test will possess the requisite physicochemical attributes.(Ali et al., 2015)

FACTORS AFFECTING TRANSDERMAL DRUG DELIVERY

Numerous factors can influence the effectiveness of transdermal drug delivery. These can be categorized into several main areas:

1. **Drug Properties**: The properties of the drug itself play a significant role in its potential for transdermal delivery. The drug must have the appropriate size, lipid solubility, and partition coefficient to penetrate the skin's outer layer (stratum corneum). The drug should also have a low molecular weight (under 500 Dalton), and its melting point should not be excessively high. Besides, the drug should be effective in low concentrations to ensure that a sufficient amount can be delivered transdermally. (Isaac &Holvey, 2012)
2. **Skin Condition**: The skin's state greatly affects transdermal drug delivery. Factors such as skin thickness, hydration level, temperature, and the presence of hair or sweat glands can influence the drug absorption rate. Skin conditions like dermatitis or psoriasis may also impact the effectiveness of transdermal drug delivery.
3. **Formulation Factors**: The components of the transdermal patch or system can also affect the drug delivery. These may include the use of penetration enhancers, the type of drug reservoir, the adhesive used, and the design of the system. The formulation should be designed to promote optimal drug release and absorption.
4. **Patient Factors**: Age, gender, ethnicity, and individual metabolic differences can all affect how a drug is absorbed and used in the body. Therefore, these factors can also impact the effectiveness of transdermal drug delivery.
5. **Physical Factors:** Physical activities like exercising can increase the blood flow rate and body temperature, which may accelerate the drug absorption process. Conversely, activities that may cause friction to the application site can potentially dislodge the transdermal patch, disrupting drug delivery.(Wiechers, 1989)
6. **Environmental Factors:** Environmental parameters such as temperature and humidity can influence the rate of drug diffusion through the skin. For example, high humidity levels can increase skin hydration, potentially enhancing the permeability of the skin to the drug.
7. **Biological Factors:** Biological factors like the individual's health status and skin integrity can play a major role. Diseases, especially those affecting skin health or metabolic processes, can influence the effectiveness of transdermal drug delivery. Inflamed or damaged skin may have altered permeability, which could impact drug absorption rates.(Liuzzi et al., 2016)

BASIC COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEMS

a. Polymer matrix/drug reservoir
b. Membrane
c. Drug
d. Permeation enhancers
e. Pressure-sensitive adhesives (PSA)
f. Backing laminates
g. Release liner
h. Plasticizers and solvents

a. Polymer matrix/drug reservoir

Polymers serve as the fundamental structure of Transdermal Drug Delivery Systems (TDDS), governing the discharge of drugs from the apparatus. The formulation of a polymer matrix is usually accomplished by dispersing the drug in a liquid or solid synthetic polymer foundation. For use in TDDS, polymers should demonstrate biocompatibility and chemical compatibility with the drug as well as other system components like penetration boosters and pressure-sensitive adhesives (PSAs). They should also ensure consistent and effective administration of a drug throughout the product's intended duration of use while maintaining safety standards.(Cherukuri et al., 2017)

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Table 01: Polymers used in TDDS

Natural Polymers	Synthetic Elastomers	Synthetic Polymers
Collagen	Polybutadiene	Polyethylene (LDPE, HDPE)
Chitosan	Polyisoprene	Polypropylene
Polysaccharides (Starch, Cellulose)	Polychloroprene (Neoprene)	Polysiloxanes (PDMS)
Gelatin	Silicone Elastomers	Polyvinyl Chloride (PVC)

When choosing the polymer for use in the transdermal system, the following specifications should be taken into account:

- The polymer's molecular weight, glass transition temperature, and chemical functionality should facilitate suitable diffusion and subsequent release of the specified drug.
- The polymer should be stable, inert with respect to the drug, readily manufacturable and capable of being fabricated into the intended product, and cost-effective.
- The polymer, as well as its degradation byproducts, must be harmless or non-antagonistic to the host organism.
- The polymer's mechanical attributes should maintain stability even when considerable amounts of active ingredients are integrated into it.

b. Membrane

Membranes are fundamental components in the construction of transdermal patches, utilized either as a solitary layer in the patch assembly or sealed to the backing to create a pocket that houses the drug-infused matrix. These membranes are instrumental in regulating the availability of the drug and/or excipients to the skin by leveraging their diffusion characteristics. Some common materials utilized for creating these rate-controlling membranes include ethylene vinyl acetate, silicone rubber, and polyurethane.(Ganti et al., 2018a)

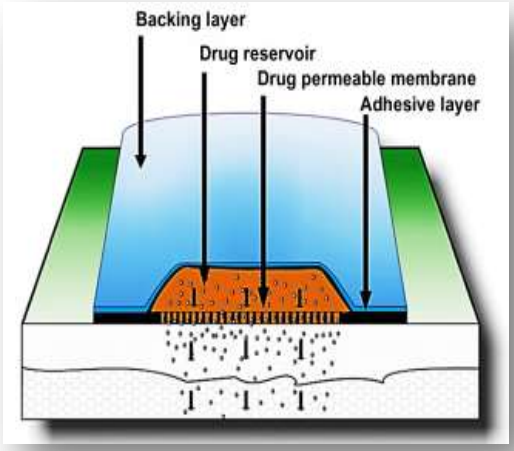

Figure 04: Basic Components of transdermal drug delivery Systems

c. Drug

The process of developing a successful Transdermal Drug Delivery System (TDDS) necessitates judicious selection of the drug. Transdermal patches present numerous advantages for certain types of drugs such as those prone to extensive first-pass metabolism, those with a narrow therapeutic window, or those with a short half-life, which might lead to patient non-adherence due to the need for frequent dosing.(Shingade, 2012)

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Table 02: Ideal properties of Drugs for TDDS

Parameters	Properties
Dose	Should be low (less than 20 mg/day)
Half-life	10 or less (h)
Molecular weight	<400 Da
Partition coefficient	Log P (octanol–water) between 1.0 and 4.0
Skin permeability coefficient	$>0.5 \times 10^{-3}$ cm/h
Liophilicity	10 < Ko/w < 1000
Oral bioavailability	Low
Therapeutic index	Low
Melting point	<200°C
pH	Between 5.0 and –9.0

Table 03: Factors to be considered for transdermal dose calculation

Physiochemical	Pharmacokinetic	Biological
Solubility	Half-life	Skin toxicity
Crystallinity	Volume of distribution	Site of application
Molecular weight	Total body clearance	Allergic reaction
Polarity	Therapeutic plasma concentration	Skin metabolism
Melting point	Bioavailability factor	Skin permeability

Several drugs have proven suitable for transdermal delivery, including Nicardipine hydrochloride, Captopril, Atenolol, Metoprolol tartarate, Clonidine, Indapamide, Propranolol hydrochloride, Carvedilol, Verapamil hydrochloride, and Niterdipine, among others.

d. Permeation enhancers

A long-established strategy for augmenting Transdermal Drug Delivery (TDD) employs the use of penetration enhancers, also known as sorption promoters or accelerants. These substances augment the permeability of the Stratum Corneum (SC), thereby facilitating increased therapeutic concentrations of the drug of interest.

Penetration enhancers operate by interacting with the structural constituents of the SC, causing modifications to its barrier functions and subsequently leading to enhanced permeability. It is proposed that there are three potential pathways through which a drug can penetrate the skin: the polar pathway, the nonpolar pathway, and a mixed polar/nonpolar pathway.(Magnusson et al., 2001)

The action of the enhancers is centered around modifying one of these pathways. To influence the polar pathway, it is essential to induce a conformational change in proteins or instigate solvent swelling. In order to modify the nonpolar pathway, changes need to be made to the rigidity of the lipid structure, causing the crystalline pathway to become fluidized - an action that significantly enhances diffusion.

Fatty acid enhancers work by increasing the fluidity of the lipid component of the SC. Some enhancers, often referred to as binary vehicles, act on both polar and nonpolar pathways, modifying the multilaminate pathway for penetrants.

Approaches to modifying the barrier properties of the SC, in order to augment drug penetration and absorption through the skin, can be primarily classified into two categories:

- Chemical methods,
- Physical methods of enhancement.

Chemical methods

Chemicals that facilitate the penetration of drugs applied topically are typically referred to as penetration enhancers, absorption promoters, or accelerants. These chemical enhancers perform several functions:

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- They can enhance and optimize the thermodynamic activity of the drug when functioning as a co-solvent.
- They can amplify the partition coefficient of the drug, promoting its release from the vehicle into the skin.
- They can condition the Stratum Corneum (SC) to foster drug diffusion.
- They can promote penetration and create a drug reservoir within the SC.

Desirable characteristics of penetration enhancers operating within the skin include:

- Non-toxicity, non-irritating, and non-allergenic properties.
- Rapid action, with the activity and duration of the effect being predictable and reproducible.
- They should possess no pharmacological activity within the body, meaning they should not bind to receptor sites.
- Unidirectional functioning, allowing therapeutic agents into the body while preventing the loss of endogenous material.
- Rapid and complete restoration of skin barrier properties once removed.
- Suitability for formulation into various topical preparations, implying compatibility with both excipients and drugs.
- Cosmetic acceptability, with a suitable skin "feel".

Among the most extensively studied permeation enhancers are sulphoxide (DMSO), fatty acids (such as oleic acid), alcohol (like methanol), glycol (specifically propylene glycol), surfactant (anionic surfactant), and azone (lauracapram).(Kogan &Garti, 2006)

Physical enhancers

Iontophoresis and ultrasound, also referred to as phonophoresis or sonophoresis, represent exemplars of physical augmentation methods employed to bolster the percutaneous penetration and absorption of an array of therapeutic agents.(Pierre & dos Santos Miranda Costa, 2011)

e. Pressure-sensitive adhesives (PSA)

Pressure-sensitive adhesives (PSAs) are substances that adhere to a substrate, such as skin, upon the application of minimal force, and upon removal, leave no residue. This adherence involves the formation of interatomic and intermolecular attractive forces at the contact point. This intimate contact necessitates the substance's ability to deform under slight pressure, hence the term "pressure-sensitive." The adhesion process involves a liquid-like flow that results in the wetting of the skin surface upon pressure application and, upon pressure removal, the adhesive solidifies in that state. For a PSA to wet and spread on the skin, its surface energy must be lower than that of the skin. The initial adhesion is followed by the build-up of a stronger PSA/skin bond, facilitated by interactions such as hydrogen bonding, which are contingent on skin characteristics and other parameters. In Transdermal Drug Delivery Systems (TDDS), PSAs like polyisobutylene-based adhesives, acrylics, and silicone-based PSAs, and hydrocarbon resin are commonly used. These can either be situated around the TDDS edge or laminated as a continuous adhesive layer on the TDDS surface. The PSA should exhibit compatibility with the drug and excipients, as their presence can alter the mechanical characteristics of the PSA and the drug delivery rate.

Backings, selected based on appearance, flexibility, and occlusion necessity, are critical in TDDS design, with the chemical resistance of the material being of utmost importance. The compatibility of excipients must also be considered as prolonged contact may induce the leaching of additives from the backing layer or may prompt the diffusion of excipients, drugs, or penetration enhancers through the layer. Optimal backing exhibits low modulus or high flexibility, excellent oxygen transmission, and a high moisture vapor transmission rate. Examples of backing materials include vinyl, polyethylene, polyester films, aluminum, and polyolefin films.(Shi et al., 2014)

During storage, a protective liner covers the patch, which is discarded before the patch's application to the skin. Given the liner's intimate contact with the TDDS, it must be chemically inert. Release liners typically consist of a base layer, which could be either nonocclusive (e.g., paper fabric) or occlusive (e.g., polyethylene, polyvinyl chloride), and a release coating layer, usually composed of silicon or Teflon. Other materials used for TDDS release liners include polyester foil and metalized laminates.(Cho et al., 2009)

TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEMS

1. **Single-layer Drug-in-Adhesive Patches:** These are the simplest type of transdermal patches. The patch consists of a single layer of an adhesive matrix that contains the drug. The adhesive matrix not only holds the components together but also serves as the releasing

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medium for the drug. Once applied, the drug diffuses through this adhesive layer onto the skin.(Gao et al., 2009)

2. **Multi-layer Drug-in-Adhesive Patches:** These are an extension of the single-layer patches and typically include one or more drug-containing layers and other layers for control of drug delivery, often sandwiched between an impermeable backing layer and a protective release liner.(Gao et al., 2009)
3. **Reservoir Patches:** These patches have a separate drug reservoir, which is encapsulated between an impermeable backing and a rate-controlling membrane. The drug seeps from this reservoir at a controlled rate and then through the skin. They often include an adhesive layer around the reservoir to adhere to the skin.(Hadgraft& Lane, 2006)
4. **Matrix Patches:** These patches contain the drug distributed throughout a polymer matrix, from which the drug diffuses out onto the skin. The matrix may be adhesive itself or may be surrounded by an adhesive layer.(Hadgraft& Lane, 2006)

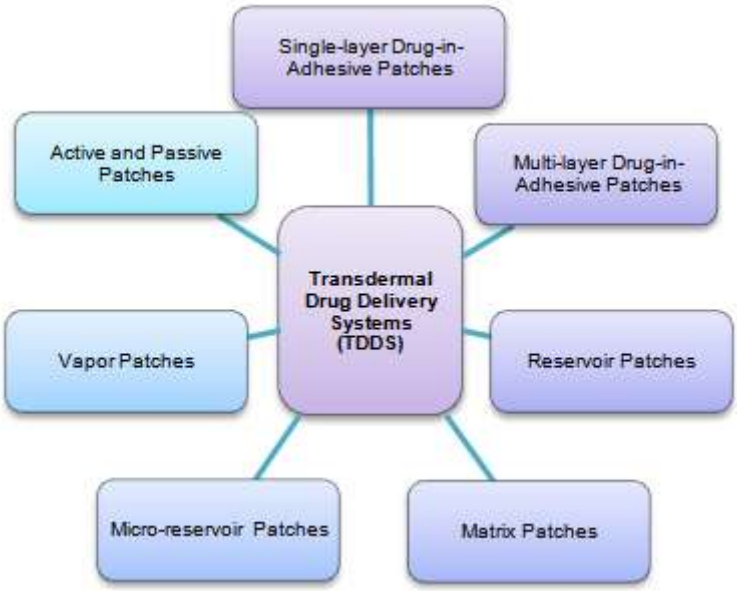

Figure 05: Types of transdermal Drug Delivery Systems

5. **Micro-reservoir Patches:** These are a combination of the reservoir and matrix systems. The drug is suspended in an aqueous solution and then mixed into a polymer to form thousands of microscopic reservoirs of drug solution within the polymer matrix.(Kusum Devi et al., 2003)
6. **Vapor Patches:** Vapor patches are designed to release the drug in vapor form. The drug often used in these types of patches is typically for decongestion purposes and releases a vapor which is inhaled to clear up congestion.(Kusum Devi et al., 2003)
7. **Active and Passive Patches:** Passive patches, which are the most common type, rely on the body's heat and natural skin permeability to deliver the drug. Active patches, on the other hand, use technologies such as iontophoresis, sonophoresis or microneedles to actively enhance drug delivery across the skin barrier.(Singh &Maibach, 1994)

Evaluation of transdermal drug delivery systems

Interaction studies

Almost all pharmaceutical dosage forms incorporate excipients as vital components. Among other factors, the formulation's stability is determined by the drug's compatibility with these excipients. For a stable product to be formed, the drug and excipients need to be compatible; hence, it's essential to identify any potential physical or chemical interactions that could influence the drug's bioavailability and stability. When the excipients are novel and haven't been utilized in formulations with the active ingredient, compatibility studies become a critical part of formulation development. Techniques used for interaction studies often include thermal analysis,

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Fourier Transform Infrared spectroscopy, UV spectroscopy, and various chromatographic methods. These studies typically compare the physicochemical properties of the substances, such as assay, melting endotherms, characteristic wave numbers, absorption maxima, and so on.(Mittal et al., 2009)

Patch Thickness

Utilizing a digital micrometer, the thickness of the drug-infused patch is assessed at various points. By calculating the average thickness and standard deviation, the prepared patch's thickness is ensured.(Nair et al., 2013)

Weight Uniformity

Prior to testing, the prepared patches are dried at 60°C for a duration of 4 hours. A specific portion of the patch is cut from different sections and weighed using a digital balance. The average weight and standard deviation values are determined from these individual weights.(Nair et al., 2013)

Folding Endurance

A strip of the patch, of a defined area, is cut evenly and repeatedly folded at the same location until it breaks. The number of folds the film can withstand at the same place before breaking indicates the folding endurance value.(Nair et al., 2013)

Percentage Moisture Content

Individual films from the prepared patches are weighed and placed in a desiccator with fused calcium chloride at room temperature for a 24-hour period. Following this period, the films are reweighed to ascertain the percentage of moisture content using the specified formula below:

Percentage Moisture Content = [(Initial weigh – Final weight)/Final weight] x 100

Percentage Moisture Uptake(Nair et al., 2013)

The individual films are weighed and placed in a desiccator at room temperature for a duration of 24 hours. The desiccator contains a saturated solution of potassium chloride to maintain a relative humidity (RH) of 84%. Following this period, the films are reweighed to establish the percentage moisture uptake, determined by the formula provided below:

Percentage Moisture Uptake = [(Final weigh – Initial weight) / Initial weight] x 100

Evaluation of Water Vapor Permeability (WVP)

The determination of WVP employs the foam dressing method, where the conventional air-forced oven is substituted with a natural air circulation oven. WVP can be calculated with the following formula:

$WVP = W / A$

Here, WVP is expressed in gm/m^2 per 24 h, 'W' represents the quantity of vapor that has permeated through the patch (expressed in gm/24 h), and 'A' stands for the exposed surface area of the samples (expressed in m^2).

Drug Content Determination

A specific portion of the patch is dissolved in an appropriate solvent in a designated volume. The solution is then filtered through a filter medium and the drug content is assessed using a suitable method (either UV or HPLC technique). The provided value represents the average from three different samples.(Akram et al., 2018)

Uniformity of Dosage Unit Test

A precise weight of the patch is cut into small pieces and transferred into a particular volume using a volumetric flask. This is dissolved in a suitable solvent and sonicated to ensure complete drug extraction from the patch, which is then made up to the mark with the same solvent. The resultant solution is allowed to settle for approximately 1 hour, after which the supernatant is suitably diluted to achieve the desired concentration with the appropriate solvent. This solution is then filtered using a 0.2-µm membrane, and analysed using an appropriate analytical technique (UV or HPLC). The drug content per piece is then calculated.(Aggarwal et al., 2012)

Polariscope Examination

This test aims to inspect the drug crystals in the patch using a polariscope. A specific surface area of the piece is placed on the object slide, and observation is made for the drug crystals to distinguish whether the drug is present in a crystalline or amorphous form within the patch.

Shear Adhesion Test

This test measures the cohesive strength of an adhesive polymer, which can be influenced by the molecular weight, the degree of cross-linking, the polymer's composition, and the type and quantity of tackifier added. An adhesive-coated tape is applied onto a stainless-steel plate; a specified weight is hung from the tape which

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applies a pulling force in a direction parallel to the plate. The shear adhesion strength is determined by timing the duration it takes to pull the tape off the plate. A longer removal time indicates greater shear strength.(Jafri et al., 2019)

Peel Adhesion Test

This assessment measures the force necessary to dislodge an adhesive coating from a test substrate, which is defined as peel adhesion. The peel adhesion properties are dependent on the molecular weight of the adhesive polymer and the type and quantity of additives incorporated. A single tape is attached to a stainless-steel plate or a chosen backing membrane, then the tape is peeled off the substrate at an angle of 180º. The force required for this removal is recorded.(Minghetti et al., 2004)

Thumb Tack Test

This is a qualitative procedure employed to determine the tack property of the adhesive. The thumb is pressed against the adhesive, facilitating the relative tack property detection.(Minghetti et al., 1999)

Flatness Test

Three longitudinal strips from different parts of each film are cut - one from the center, one from the left side, and another from the right side. The length of each strip is measured, and any variation in length due to nonuniform flatness is determined by calculating the percent constriction, where 0% constriction is equivalent to 100% flatness.(Ganti et al., 2018b)

Percentage Elongation Break Test

The percentage elongation break is calculated by recording the length just prior to the breakpoint. The percentage elongation can be ascertained using the following formula:

Elongation percentage = (L1 - L2) / L2 × 100

Rolling Ball Tack Test

This test is utilized to assess the softness of a polymer, which correlates with tackiness. In this evaluation, a stainless-steel ball of 7/16 inches in diameter is released from an inclined track, which then rolls down and makes contact with the adhesive surface, facing upward and horizontal. The distance the ball travels across the adhesive is taken as a measure of tack, and it is presented in inches.

Quick Stick (Peel-Tack) Test

This test involves pulling the tape away from the substrate at an angle of 90º at a speed of 12 inches per minute. The force of peel required to rupture the bond between the adhesive and the substrate is measured and denoted as the tack value. This is usually expressed in units of ounces or grams per inch width.

Probe Tack Test

In this test, a clean probe with a defined surface roughness is brought into contact with the adhesive. Once a bond is formed between the probe and the adhesive, the probe is removed, mechanically breaking the bond. The force required to pull the probe away from the adhesive at a fixed rate is noted as tack, and it is expressed in grams.

In Vitro Drug Release Studies

For evaluating the drug release from the created patches, the paddle over disc method (USP apparatus V) can be implemented. Films of established thickness are cut into a specific shape, weighed, and affixed onto a glass plate using an adhesive. The glass plate is then immersed in 500 mL of dissolution medium or phosphate buffer (pH 7.4), with the apparatus maintaining a temperature of 32 ± 0.5°C. The paddle is positioned at a distance of 2.5 cm from the glass plate and is set to operate at 50 rpm. At predetermined time intervals over 24 hours, samples (5-mL aliquots) are collected and examined using UV spectrophotometry or HPLC. This experiment should be conducted in triplicate, and the average value should be computed.(Latif et al., 2021)

In Vitro Skin Permeation Studies

In vitro permeation study can be conducted employing diffusion cells. Abdominal skin of male Wistar rats weighing 200–250 g is preferred. Hair from the abdominal area is carefully removed using an electric clipper; any adhering tissues or blood vessels are thoroughly cleaned off the dermal side of the skin with distilled water. The skin is then equilibrated for an hour in dissolution medium or phosphate buffer at pH 7.4 before the experiment begins, and it is placed on a magnetic stirrer with a small magnetic needle to ensure uniform distribution of the diffusant. The temperature of the cell is sustained at 32 ± 0.5°C by using a thermostatically controlled heater. The harvested rat skin piece is mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor

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compartment. Specified volumes of the sample are taken from the receptor compartment at regular intervals, replaced with an equivalent volume of fresh medium. Samples can be filtered and analyzed spectrophotometrically or with HPLC. Flux can be determined as the slope of the curve between the steady-state values of the amount of drug permeated (mg/cm^2) against time in hours, and permeability coefficients can be calculated by dividing the flux by the initial drug load (mg/cm^2).(Abd et al., 2021)

Skin Irritation Study

Skin irritation and sensitization evaluations can be executed on healthy rabbits, with an average weight of 1.2–1.5 kg. The dorsal surface (50 cm^2) of the rabbit is cleaned and shaven to remove hair. The area is further cleaned with rectified spirit, followed by the application of the test formulations on the skin. After a period of 24 hours, the patch is removed, and the skin is inspected and rated into five categories based on the severity of any observed skin damage. (Akhlaq et al., 2021)

Stability Studies

Stability studies should follow the ICH guidelines, storing the Transdermal Drug Delivery System (TDDS) samples at conditions of 40 ± 0.5°C and relative humidity of 75 ± 5% over a 6-month period. The samples should be retrieved and suitably analyzed for drug content at 0, 30, 60, 90, and 180-day intervals. (Jeong et al., 2021)

Advancements in transdermal drug delivery systems

1. **Advances in Microneedle Technology for Transdermal Delivery**: Microneedles are a novel technology that enhances transdermal drug delivery. They are micro-sized needles designed to pierce the skin's epidermal layer, creating micro-channels that allow drug absorption without causing pain, bleeding, or infection. There are various types of microneedles such as solid, hollow, dissolving, and coated, each designed for different drug delivery mechanisms and applications. (Nagarkar et al., 2020)
2. **Progress in Transdermal Nanocarriers and Nanotechnology**: Nanotechnology has revolutionized transdermal drug delivery, particularly through the development of nanocarriers. These tiny structures can efficiently encapsulate drugs and facilitate their penetration into the skin, enhancing the efficacy of transdermal drug delivery. (D. Yang et al., 2021)
3. **Improvements in Skin Permeation Enhancers**: Skin permeation enhancers improve the skin's ability to absorb drugs. These substances work by temporarily disrupting the skin's barrier function, allowing for greater drug penetration. The recent advancements focus on finding safer and more effective enhancers. (Ahad et al., 2021)
4. **Evolving Role of Nanogels and Hydrogels in TDDS**: Nanogels and hydrogels have been increasingly used in TDDS due to their biocompatibility, tunable drug release profiles, and ability to encapsulate a variety of drug molecules. These materials can help improve patient compliance and treatment effectiveness. (Uchida et al., 2021)
5. **Developments in Ultrasound-Mediated Transdermal Drug Delivery**: Ultrasound has been found to temporarily disrupt the skin's barrier, allowing drugs to penetrate more effectively. Recent advancements have focused on optimizing ultrasound parameters to maximize drug delivery while minimizing skin damage. (D. Yang et al., 2021)
6. **The Rise of Bioresponsive Transdermal Systems**: Bioresponsive systems can respond to physiological cues such as pH, temperature, or biomolecules, to regulate drug release. They offer potential for personalized therapy by adjusting drug delivery according to the patient's needs. (Jain et al., 2021)
7. **Advancements in Wearable Transdermal Delivery Devices**: These are devices that can be worn on the skin to deliver drugs over an extended period. Advancements have focused on improving the comfort, ease of use, and drug delivery efficiency of these devices. (Yu et al., 2021)
8. **Progress in Iontophoresis and Electroporation Techniques**: Both techniques use electrical currents to enhance transdermal drug delivery. Recent advancements are focused on optimizing the parameters of the electric current to increase drug delivery while minimizing skin irritation. (D. Yang et al., 2021)
9. **Innovations in Heat-Assisted Transdermal Drug Delivery**: This technique uses heat to enhance skin permeability and drug absorption. Recent advancements aim to

optimize the heat application to improve drug delivery and patient comfort.

10. **Advances in 3D Printing for Transdermal Patches**: 3D printing technology offers the potential for personalized transdermal patches, where the drug dose, release profile, and patch size can be tailored to individual patients. (Q. Yang et al., 2021)
11. **Nanostructured Lipid Carriers (NLCs) in TDDS**: NLCs are advanced drug delivery systems that offer benefits like improved drug stability, controlled drug release, and enhanced skin penetration. They are increasingly being used in transdermal drug delivery systems. (Araujo et al., 2021)
12. **Breakthroughs in Transdermal Vaccine Delivery**: Transdermal delivery of vaccines is a promising area of research. It offers potential benefits such as needle-free administration, self-administration, and improved vaccine efficacy. (Menon et al., 2021)
13. **Advancements in the Design of Transdermal Biosensors**: Transdermal biosensors are devices that can monitor physiological parameters or detect specific biomolecules directly through the skin. They are becoming more sophisticated, with advancements focusing on improving sensitivity, specificity, and miniaturization. (Jung &Jin, 2021)

II. CONCLUSION

TDDS represents a novel development in the field of dosage forms for many injectable and orally delivered drugs that possess suitable physicochemical and pharmacological properties. TDDS ensures that a pharmacologically active compound reaches the pertinent in vivo location with minimal side effects. Owing to the various benefits of TDDS, numerous research initiatives are underway to incorporate new drugs into the system. Various devices that aid in enhancing the absorption rate and penetration of the drug are also under investigation. TDDS heavily rely on components such as polymers, penetration enhancers, backing laminates, plasticizers, and liners to ensure effective adhesion and controlled drug release to the systemic circulation via the skin over an extended period. Transdermal patches can be categorized into various systems, including reservoir system, matrix system, and micro reservoir system. Upon the creation of transdermal patches, standardized methodologies are utilized to evaluate various parameters. Due to recent technological advancements and the ability to deliver drugs to the site of action without disrupting the skin membrane, transdermal delivery is fast becoming the preferred route of drug administration. This mode of delivery surpasses the challenges associated with conventional drug delivery methods, thus exhibiting a promising future. As per the duration of therapy, various drugs are commercially available in the form of transdermal patches.

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