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An Update On Transdermal Drug Delivery System (TDDS): A Review

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ABSTRACT

Transdermal medication administration has become a proven technology in the previous two decades, offering a variety of advantages over the conventional approach. Because transdermal medication delivery allows for regulated and predefined drug distribution into the patient, as well as the ability to easily cease drug action when necessary. Small, lipophilic, low-dose medicines were administered using first-generation transdermal administration. In second-generation transdermal delivery, the medicine was delivered via ultrasound, iontophoresis, and chemical enhancers. Microneedles, electroporation, thermal ablation, and microdermabrasion were employed in third-generation transdermal drug delivery. This review focuses on the numerous modules utilised in medication administration via topical application. The primary goal of a transdermal medication delivery method is to transfer the drug into systemic circulation with minimum inter and intracellular interactions.

Keywords: *Transdermal Medication, Modern Drug Delivery Systems, Transdermal Drug Delivery.*

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INTRODUCTION

Compared to the previous two decades, innovations in drug delivery are occurring at a far faster rate. Patient compliance has improved, and Effectiveness is a crucial component of modern drug delivery systems. [1,2] Exploring innovative interfaces for therapeutic introduction on the body has been a more extreme strategy. Transdermal drug delivery is one method that uses the skin as a point of entry for medication molecules to enter the body. [3] One method of controlled drug delivery is the transdermal drug delivery system (TDDS), which aims to distribute the drug through the skin at a predetermined and regulated rate. The systemic circulation is reached using TDDS, which are adhesive drug-containing devices with a predetermined surface area that release a predetermined amount of drug to the surface of intact skin at a predetermined rate. [4,5] By improving patient compliance and avoiding first-pass metabolism, respectively, transdermal administration offers a competitive advantage over injectables and oral methods. [6,7] Since oral treatment involves introducing a fixed dose at regular intervals to achieve and maintain drug concentration in the body within a therapeutically effective range, causing the drug concentration in the body to follow a peak and trough profile, increasing the risk of adverse effects or therapeutic failure, transdermal route has competed with oral treatment as the most successful innovative research area in drug delivery. Transdermal drug administration through intact skin can closely mimic the advantages of intravenous drug infusion, such as bypassing hepatic "first pass" hepatic elimination (HEPE) to maintain constant prolonged and therapeutically effective drug levels in the body, without its potential risks. [8-10] The advantages and disadvantages of medication delivery over the skin for systemic therapy are shown in Table 1. [5,11-13]

Drug and skin penetration

It is crucial to review the structural and biochemical characteristics of human skin as well as those that affect the barrier function and the rate of drug absorption into the body through the skin because the goal of TDDS is to achieve systemic medication through topical application on intact skin.

The epidermis and dermis, or corium, are the two anatomically distinct layers of the skin that are perforated by gland ducts and hair shafts, respectively [Figure 1]. One of the largest organs in the human body, the skin covers an average adult human's body surface area of around 2 m2. The fatty subcutaneous layer (hypodermis), the connective tissue-rich dermis, and the stratified avascular cellular epidermis are the three main skin layers, from the inside out. One-third of the blood that circulates through the body is received by this complex organ. The epidermis, which is roughly 150 m thick, is

produced by an active population of epithelial basal cells. It is the skin's topmost layer, and as a result of differentiation, cells move from the basal layer up towards the skin's surface. Because the epidermis lacks blood vessels, nutrients and waste products must diffuse across the dermal-epidermal junction in order to keep the epidermis healthy. Five layers make up the epidermis: the stratum germinativum (base layer), stratum spinosum (spinous layer), stratum granulosum (granular layer), stratum lucidum, and stratum corneum (SC), which are listed in order from the inside to the outside. The epidermis without the SC is typically referred to as the viable epidermis because the SC cells are dead. For the majority of compounds, the SC is thought to be the rate-limiting barrier in transdermal penetration. The SC is made up of 15–20 layers of corneocytes (terminally developed keratinocytes) packed with keratin and anchored in a lipophilic matrix. The lipids of this extracellular matrix are unique in many ways, including the following: (1) they provide the only continuous phase (and diffusion pathway) from the skin surface to the base of the SC; (2) the composition (ceramides, free fatty acids, and cholesterol) is distinct among biomembranes; (3) despite the lack of polar bilayer-forming lipids, the SC lipids exist as multilamellar sheets; and (4) the predominant lipid type is cholesterol. The SC is 10-15 m thick when it is dry; when it is hydrated, the SC expands and becomes up to 40 m thick. The SC is sometimes represented as a brick-and-mortar structure, with the keratin-rich corneocytes serving as the bricks and the intercellular lipid-rich matrix as the mortar.

The dermis, which is of mesoderm origin, forms the base of a firm of connective tissue upon which the epidermis is formed. In the superficial levels, elastic tissue is mixed in with bundles of collagen fibres to form the dense network of connective tissue that makes up the dermis or corium. Fine plexuses of blood arteries, lymphatics, nerves, hair follicles, sweat glands, and sebaceous glands can all be found in the dermis. [8,9,14,15]

Table 1 lists the Advantages and Disadvantages of TDDS.

Advantages

- Self-administration is conceivable, and the drug can be released continuously and steadily**.**
- Avoids longer and multiday dosage intervals, peak and trough medication levels, and.
- Prevents gastrointestinal irritation, enzymatic breakdown via the digestive tract, and first-pass hepatic metabolism.
- Patient compliance is improved with less frequent dosage.
- Patients who are unable to take oral medication should consider an alternative route
- Vomiting or diarrhoea do not alter the delivery of doses.

Disadvantages

- Currently, only tiny lipophilic medications can be administered through the skin.
- Because patch size restricts the amount that can be delivered, the drug molecule needs to be powerful.
- Not suitable for high drug doses.
- Adhesion may vary with patch type and environmental conditions.
- Adhesion may vary with patch type and environmental conditions.
- The barrier functions of the skin change from one site to another on the same person, from person to person and with age.

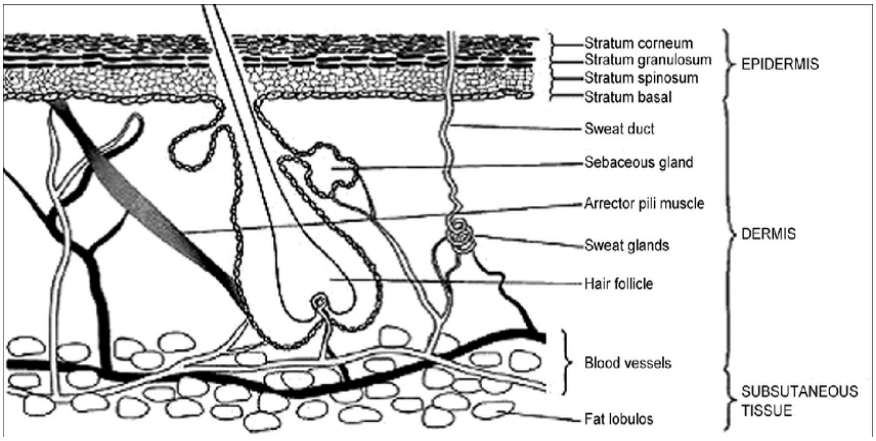

Figure 1: Cross-section view of human skin showing different cell layers and appendages

ROUTES OF PENETRATION

A drug molecule can traverse the intact SC in one of three key ways: by skin appendages (shunt pathways), across the intercellular lipid domains, or via a transcellular route. [Fig. 2]. The flow of a certain medicine to permeate by a mixture of these routes is controlled by the physiochemical characteristics of the molecule.[5,9]

The Appendageal Route

The transappendageal routes, often referred to as the shunt routes, allow substances to pass via sweat glands and through hair follicles and the sebaceous glands that are located nearby. Appendages of the skin offer a continuous path directly through the SC barrier. The long-held belief that the follicles take up roughly 0.1% of the surface area of the human skin has been reexamined in recent studies. The forehead offers 13.7 mm2/cm2 as the follicular infundibula, or roughly 13.7% of the surface area of the forehead is available as follicles, according to research by Otberg et al. that demonstrated the importance of the follicular number, opening diameter, and volume in drug delivery through these appendages. A fascinating finding from the same study was that forearm skin seemed to support the conventional wisdom that follicles provide about 0.1% of the SC.

Transcellular route

Drugs that penetrate the skin transcellularly pass via corneocytes on their way in. The keratin in corneocytes, which are highly hydrated, creates an aquatic environment from what drugs are hydrophilic and can pass. The transcellular pathway necessitates partitioning into, diffusion through, and across the intercellular lipids in addition to the keratin bricks.

Intercellular route

The medication diffuses through the continuous lipid matrix when travelling between cells. This approach is a major challenge for two reasons: (i) Recalling the "bricks and mortar" SC paradigm, the interdigitating characteristics of corneocytes produce a complex track for intercellular drug absorption, as opposed to the transcellular route's comparatively direct approach. (ii) Alternating structured bilayers make up the intercellular domain. A medication must therefore successively partition into and permeate through numerous aqueous and lipid domains. It is widely acknowledged that this pathway is the most typical way for tiny, uncharged compounds to penetrate skin.

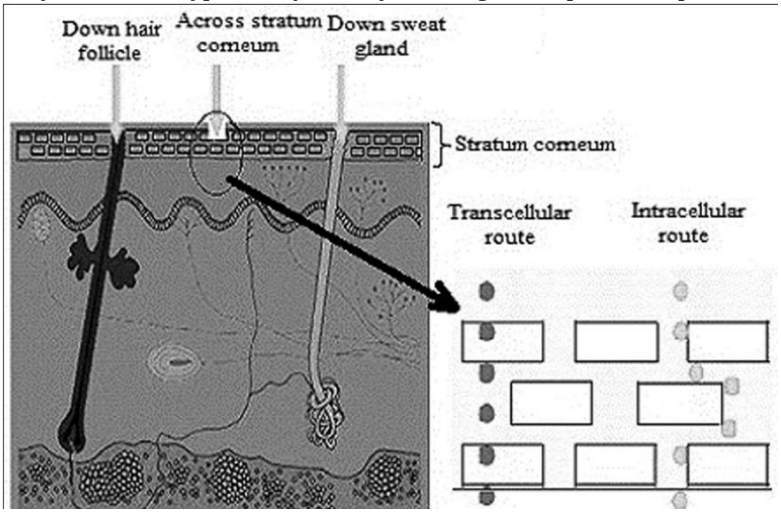

Figure 2: Drug penetration pathways across skin

EVALUATION PARAMETERS

Interaction studies

Excipients are essential parts of practically all dose forms used in pharmaceuticals. The compatibility of the medicine with the excipients is one of the elements that affects a formulation's stability. To create a stable product, the drug and excipients must be compatible with one another. As a result, it is essential to identify any potential physical or chemical interactions because they may impair the bioavailability and stability of the medication. The compatibility studies are crucial for formulating new excipients that have never been used in formulations containing the active ingredient. By contrasting their physicochemical properties, such as assay, melting endotherms, distinctive wave numbers, absorption maxima, etc., interaction studies are frequently conducted in thermal analysis, FT-IR, UV, and chromatographic procedures.[16,17]

Thickness of the patch

A digital micrometre is used to measure the thickness of the drug-loaded patch at various spots, calculating the average thickness and standard deviation for the same to guarantee the prepared patch's thickness. [18]

Weight uniformity

Before testing, the produced patches must be dried at 60°C for four hours. A predetermined patch area must be divided into various patches and weighed using a digital balance. The individual weights must be used to obtain the average weight and standard deviation values. [18]

Folding endurance

It is necessary to cut a strip of a particular width uniformly and fold it repeatedly until it breaks. The value of folding endurance was determined by how many times the film could be folded in the same location without breaking.[18]

Percentage Moisture content

The produced films must be weighed separately and maintained at room temperature in a desiccator with fused calcium chloride for 24 hours. The films must be reweighed after 24 hours to calculate the percentage moisture content using the procedure below. [18]

[Initial weight - Final weight / Final weight] / 100 is the formula for percentage moisture content.

Percentage Moisture uptake

To maintain 84% RH, the weighed films must be stored in a desiccator for 24 hours at room temperature with a saturated potassium chloride solution. The films must be reweighed after 24 hours to calculate the percentage moisture uptake using the technique below. [19]

[Final weight- Initial weight/Initial weight] / 100 is the percentage of moisture uptake.

Water vapour permeability (WVP) evaluation

A natural air circulation oven is used in place of an air forced oven to measure the water vapour permeability. The formula below can be used to determine the WVP.

WVP=W/A

Where WVP is stated in gm/m2 per 24 hours, A is the surface area of the exposure samples expressed in m2, and W is the amount of vapour permeated through the patch in gm/24 hours. [20]

Drug content

In a suitable solvent, a predetermined patch area must dissolve in a predetermined volume. After that, the solution must be filtered through a filter medium so that the drug content may be determined using the appropriate technique (UV or HPLC).

Each number is the average of three distinct samples.[20]

Uniformity of dosage unit test

To fully extract the medicine from the patch and make up to the required amount with it, a portion of the patch that has been precisely weighed must be sliced into little pieces and transferred to a volumetric flask of a specific size, where it must be dissolved in an appropriate solvent and sonicated. After allowing the mixture to settle for about an hour, the supernatant was appropriately diluted with a suitable solvent to achieve the necessary concentration. The solution was filtered using a 0.2 cm membrane filter, and the drug content per piece was estimated after analysis using an appropriate analytical technique (UV or HPLC). [21]

Polariscope examination

The purpose of this test is to use a polariscope to study the drug crystals in the patch. To determine if a drug is present in crystalline form or an amorphous form in the patch, a specific section of the piece must be kept on the object slide and examined for drug crystals.[21]

Shear Adhesion test

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross linking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength. [21]

Peel Adhesion test

Peel adhesion is the term used in this test to describe the amount of force needed to remove an adhesive covering from a test substrate. The factors that determined the peel adhesion properties were the molecular weight of the sticky polymer, the kind and quantity of additives. A single piece of tape is placed on a stainless steel plate or other suitable backing membrane. It is then pulled away from the surface at an angle of 180 degrees, and the force needed to remove the tape is measured. [21]

Thumb tack test

It is a qualitative test used to determine the adhesive's tackiness. The relative tack feature is simply felt by pressing the thumb on the adhesive. [21]

Flatness test

Each film must have three longitudinal strips cut off it, each at a different location, such as the centre, the left, and the right. Each strip's length was measured, and the change in length due to flatness non-uniformity was quantified by calculating the percent constriction, with 0% constriction equal to 100% flatness. [22]

Percentage Elongation break test

By observing the length shortly before the break point, the percentage elongation break is to be determined. The formula below can be used to determine the % elongation.

Elongation % is equal to L1-L2 / 100 L2.

Where L1 is each strip's ultimate length and L2 is each strip's starting length. [23]

Rolling ball tack test

This test gauges how malleable a polymer related to speech is. In this test, a 7/16-inch diameter stainless steel ball is launched onto an incline track where it rolls down and makes touch with an adhesive that is horizontal and facing upward. Tack is measured in inches and is determined by how far the ball moves along the adhesive. [24]

Quick Stick (peel-tack) test

In this test, the tape is dragged away from the substrate at a speed of 12 inches per minute at 90 degrees Celsius. The tack value, which is stated in ounces or grammes per inch width, measures and records the peel force necessary to break the binding between the adhesive and the substrate.[24]

Probe Tack test

In this test, an adhesive is brought into contact with a clean probe tip with a predetermined surface roughness, and a connection is created between the probe and the adhesive. The probe is then mechanically broken during removal. Tack, which is measured in grammes, is the force needed to draw the probe away from the adhesive at a constant rate. [24]

In vitro drug release studies

You can evaluate the drug release from the produced patches using the paddle over disc method (USP equipment V). A glass plate must be covered with dry films of defined thickness that have been cut into a specific form, weighed, and fastened with an adhesive. The device was then brought to an equilibrium temperature of 32 0.5 °C before the glass plate was submerged in 500 mL of the dissolving liquid or phosphate buffer (pH 7.4). The paddle was then turned on at a speed of 50 rpm while being placed 2.5 cm away from the glass plate. At suitable intervals up to 24 hours, samples (5-mL aliquots) can be taken out and analysed using a UV spectrophotometer or HPLC. The experiment must be run three times, and the mean value may be computed. [16]

In vitro skin permeation studies

Diffusion cells can be used to conduct an in vitro permeation research. Male Wistar rats weighing 200–250g have full thickness abdomen skin. The dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels. Before beginning the experiment, the skin was equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. A thermostatically controlled heater was used to keep the cell's temperature at 32 +/- 0.5°C. The isolated rat skin piece needs to be put in the diffusion cell between the compartments with the donor compartment's epidermis facing up. At regular intervals, a sample volume of a specific volume is to be taken out of the receptor compartment, and an equal volume of fresh medium is to be replaced. Samples must pass through a filtering media before being analysed spectrophotometrically or via HPLC. The permeability coefficients were obtained by dividing the flux by the initial drug load (mg cm-2), and flux can be calculated directly as the slope of the curve between the steady-state values of the amount of drug penetrated (mg cm-2) vs. time in hours. [16]

Skin Irritation study

Tests for skin sensitization and irritation can be carried out on healthy rabbits (average weight: 1.2 to 1.5 kg). The rabbit's dorsal surface (50 cm2) should be cleansed. The hair should be removed by shaving, and the area should be cleaned with rectified spirit before applying the appropriate formulas. After 24 hours, the patch must be removed, and the skin must then be examined and divided into 5 grades based on the degree of skin damage.[21]

Stability studies

According to ICH recommendations, stability tests must be carried out after storing TDDS samples at 40°F and 75°RH for six months. At 0, 30, 60, 90, and 180 days, the samples were removed and properly analysed for drug content. [16]

ADVANCE DEVELOPMENT IN TDDS

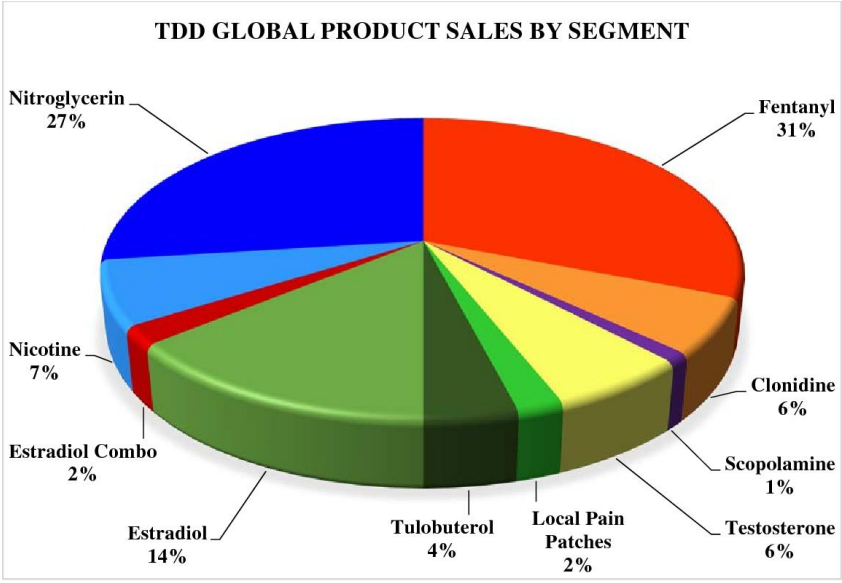

Figure 2: Global Transdermal Drug Delivery Product sales by segment

The passive transdermal administration of drugs via adhesive technology has emerged as the preferred method; adhesives and excipients are the subject of two areas of formulation study. Research on adhesives focuses on tailoring the adhesive to enhance skin adhesion during the course of use, enhance medication stability and solubility, shorten lag time, and speed up delivery. Customising the adhesive chemistry enables the transdermal formulator to maximise the efficacy of the transdermal patch because there is no universal adhesive that can handle all medication and formulation chemistries. [25]

Transdermal Drug Delivery System Market

A list of businesses that currently have transdermal medication delivery systems available on the market along with their goods and technologies. The entire range of medications administered transdermally is manufactured using 3M Pharmaceuticals' technologically advanced components, which are employed as a leader in the transdermal drug delivery industry. A graph displaying the variety of transdermal medication delivery systems now offered for sale is shown in Figure 6. The medications that are administered transdermally are plotted on the X-axis, and the proportion of all transdermal products sold on the market is plotted on the Y-axis.

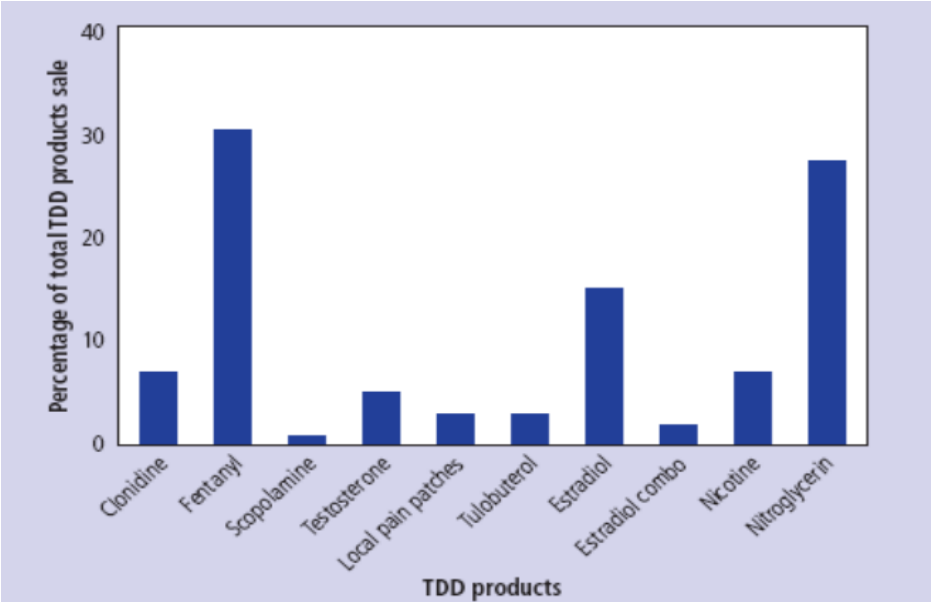

Figure 3: Graph of Transdermal Drug Delivery Products Vs. Percentage Total Sold Transdermal Drug Delivery Products.

Due to the skin acting as a barrier to drug diffusion or permeation, the spectrum of current medications that are provided utilising the transdermal drug administration approach is still restricted. [26]Active transdermal drug delivery systems, albeit relatively new to the market, are used to get over the stratum corneum barrier and are thought to have significant potential for expanding the number and types of medications that can be supplied transdermally. More than $3 billion is spent each year on transdermal drug delivery devices.[27]

Table 1: Companies and their Transdermal Drug Delivery Technologies & Products

Company Name	Transdermal Products/Technology in Market
3M Pharmaceuticals	MinitranTM, Pioneer in the field of Manufacturing Transdermal Components
Acrux Ltd.	ACROSSR, MDTSR, Patchless PatchR
Adhesives Research, Inc	ETATM, HRT Adhesives, PIB Adhesives, MTT Adhesives
Adherex Technologies, Inc.	Exherin^{TM}
Altea Therapeutics Corp.	PassPort^{R} Patch
Alza Corp.	D-Trans^{R} System, E-Trans^{R} System, Macroflux^{R} System
Antares Pharma, Inc.	ATD^{TM} Gel Technology
Biochemics, Inc.	PEN to CORER
Boehringer Ingelheim Corp.	CATAPRES-T^{TSR}
Dermisonics, Inc.	U-Strip
Elan Transdermal Technologies, Inc.	Buspirone Patch
Inovio Biomedical Corp.	MedPulser Electroporation Therapy System
ImaRx Therapeutics, Inc.	SonoDerm^{TM} Technology
Iomed, Inc.	Iontophoreris Electrodes: Trans^{QR} Flex, IOGELR, Trans^{QR} E, Optima^{AR} ; Numby Stuff ^{R}, IONTOCAINER, Phoresor^{R}
Noven Pharmaceuticals, Inc.	Vivelle^{R}, Vivelle-Dot^{TM}, Combi Patch^{TM}, Estalis ^{R}, Methy Patch^{R}
L.A.M. Pharmaceuticals LLC	IPM Wound Gel^{TM}, Polymer Matrix^{TM} Technology
Macrochem Corp.	MacroDerm^{TM}, SEPAR
Norwood Abbey Ltd.	Laser Assisted Drug Delivery(LAD), Micro-needle Drug Delivery
Sontra Medical Corp.	SonoPrep^{R}
Travanti Pharma, Inc.	Wearable Electronic Disposable Drug (WEDDR)
Vyteris, Inc.	LidoSite^{TM} Topical System

FDA Regulation and Transdermal Drug Delivery System

In 1979, the FDA approved the first transdermal drug patch.[28] Transdermal medication delivery methods have advanced significantly since that time. The developments in the field of transdermal technology and the approvals at each point in this chronology were used to create a timeline. Transdermal medication delivery systems are subject to very strict FDA regulation. According to the Food and Drug Administration's definition of a combinational device in 21 CFR 3.2(e), a transdermal drug delivery system is one.[29,30] Before a transdermal patch can be approved for usage on the market, it must first pass premarket approval (PMA), which necessitates the collection of significant evidence, such as results from biomechanical testing, animal testing, and clinical trials investigations. The Nuepro patch for the treatment of Parkinson's disease received the most recent approval in the field of transdermal drug delivery systems.[31] The component that needs to be taken into account in the passive transdermal drug delivery system is making sure the medication is there and is being administered in a controlled and stable manner, whether it is in the form of an adhesive or a drug reservoir.[32] Additionally, it's critical to comprehend how the drug interacts with the skin and confirm that the materials used to create the transdermal patch don't have any negative effects on the skin, such as itchiness, inflammation, etc. The patch must also be worn for several hours or, in certain situations, several days (such as a contraceptive patch), therefore its characteristics, such as the kind of polymers and adhesives used in its manufacture, must also be carefully taken into account. Polymers are the main component of the patch. For the creation of transdermal medication delivery systems, many types of polymeric materials are used. The polymeric materials and their properties that are employed to create transdermal drug delivery systems are described in the following portion of the study.

The Future of Transdermal Drug Delivery

According to statistical statistics, the market was valued at $12.7 billion in 2005. By 2010, that figure is expected to rise to $21.5 billion, and by 2015, it will be at $31.5 billion. TDDS is being developed by almost all pharmaceutical companies. [33] Many drugs that are administered orally or via injection may benefit from TDDS, but many drugs cannot effectively penetrate the skin membrane due to the skin barrier's low permeability. Pharmaceutical companies are now

creating novel adhesives, chemicals that improve molecular penetration and absorption, which will ultimately alter skin permeability and significantly expand the range of medications that can be administered transdermally. Iontophoresis and phonophoresis (sonophoresis), two well-known methods, are thought to achieve considerable plasma concentration levels through the epidermal membrane. For drugs delivered topically, a microneedle approach is more promising. These devices work by opening pores in the stratum cornea using a series of tiny needle-like structures, allowing drugs to be transported without being painful because the pores are not accessible to nerve ends. According to reports, these systems significantly increase the permeability of macromolecules through skin.[34]

CONCLUSION

Transdermal drug delivery systems have been employed as rational drug therapy drug delivery devices (safe, efficacious, and cost-effective). Because of the various benefits of the TDDS, many new studies are being conducted now to add newer medications into the system. A transdermal patch is made up of various fundamental components, including drug reservoirs, liners, adherents, permeation enhancers, backing laminates, plasticizers, and solvents, all of which play an important role in drug release through the skin. Various approaches are used to prepare these patches using TDDS's fundamental components. Transdermal patches are examined for physicochemical studies, in vitro permeation tests, skin irritation studies, and stability studies after they are prepared. However, before being sold, all manufactured and analysed transdermal patches must be approved by the FDA. Future TDDS advances will most likely focus on enhanced therapeutic regimen control and the further expansion of medicines accessible for use. Transdermal dose forms may allow doctors to provide more therapeutic options to their patients in order to optimise their care.

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