IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 17, Issue 1 Ser. III (Jan. –Feb. 2022), PP 43-58
www.Iosrjournals.Org

Components and systematic evaluation of Transdermal drug delivery system: A review

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Abstract
Transdermal drug delivery systems are devices with a set surface area that distribute a predetermined amount of medicine to the intact skin's surface at a predetermined rate and can be configured for extended release ranging from hours to days. Transdermal patch design and development can be explained as cutting edge. Since the emergence of transdermal treatment systems in the form of patches, the skin has become a particularly appealing route for systemic drug administration. In the realm of controlled drug delivery systems, the development of transdermal drug delivery systems (TDDS) is a game-changer. Because of their distinct advantages, transdermal dosage forms are quickly becoming a preferred alternative to traditional dosage forms. Controlled zero-order absorption, a straightforward manner of administration, and the ability to stop the activity if an unpleasant effect occurs are just a few of the benefits. The development of a transdermal drug delivery system entails a number of activities or steps, beginning with the selection of a drug molecule and continuing with the demonstration of sufficient drug flux or a pharmacokinetic study in an ex vivo and in vivo model, as well as the preparation of a drug delivery system that meets all of the drug molecule's specific needs (physicochemical, Invitro, Invivo). Complex analytical operations and multidisciplinary research is involved in transdermal studies with the evaluation of physicochemical, morphological, and textural features of the transdermal patched may be required to assess the effectiveness of transdermal medicinal devices developed for controlled drug release. This paper presents a review of Transdermal drug delivery system with different available designs with emphasis on different polymeric components of the TDDS, advantages of TDDS, typical evaluation parameters starting from adhesive evaluation of adhesive, physico chemical, In vitro, In vivo evaluation along with other analytical interaction studies.

Keywords: *Transdermal drug delivery system, Adhesives, Backing membranes, Release liners, Additives, Plasticizers, Physico-chemical evaluation, Adhesive evaluation, Invitro drug release study, Invitro skin permeation study, Franz diffusion cell, In vivo studies, Drug and PSA interaction studies.*

Date of Submission: 10-02-2022 Date of Acceptance: 24-02-2022

I. Introduction

A transdermal patch, also known as a Transdermal Drug Delivery System (TDDS), is a multi-layered, flexible pharmacological single dose preparation of varied size that contains one or more active compounds and is placed to the intact skin for systemic absorption. This is usually made with pressure-sensitive adhesives to ensure that the preparation adheres to the skin. A backing sheet, impermeable to the active material and typically impermeable to water, is included in a transdermal patch. A protective liner covers the patch's releasing surface, which must be removed before attaching the patch to the skin.

Transdermal patches are meant to slowly release the active ingredient(s) through the intact skin, resulting in a longer and consistent rate of systemic absorption. The absorption of the active ingredient through the skin is usually the rate limiting step for systemic absorption. Incorporating or dissolving the active substance in a (semi solid) reservoir with a membrane to control the release and diffusion of the active substance(s) from the patch is another option for limiting absorption. As a technique of managing drug distribution to the skin's surface, the transdermal patch can be formulated using both drug delivery principles[R-1] A Transdermal Medicine Delivery System (TDDS) is an adhesive patch that contains a drug or medication and is applied to the skin to administer specified doses trans dermally into the body over time at a predetermined rate.

Adhesive skin patches are painless and noninvasive ways to deliver medication into the body. They're simple to use, don't require injections or pills, and have a low risk of negative effects. They must be produced

with medical-grade films and adhesives that do not cause skin irritations to guarantee a controlled and exact administration of small-size Active Pharmaceutical Ingredient (API) molecules over long periods of time. [R-2]
To understand on designing and development of a Transdermal drug delivery system, it is important to know below details of Transdermal drug delivery system, viz,

- Types of TDDS
- Components of TDDS
- Advantages of TDDS and Transdermal drug absorption mechanism
- Typical evaluation parameters of TDDS
- Other Analytical evaluation of TDDS

Types of Transdermal drug delivery system

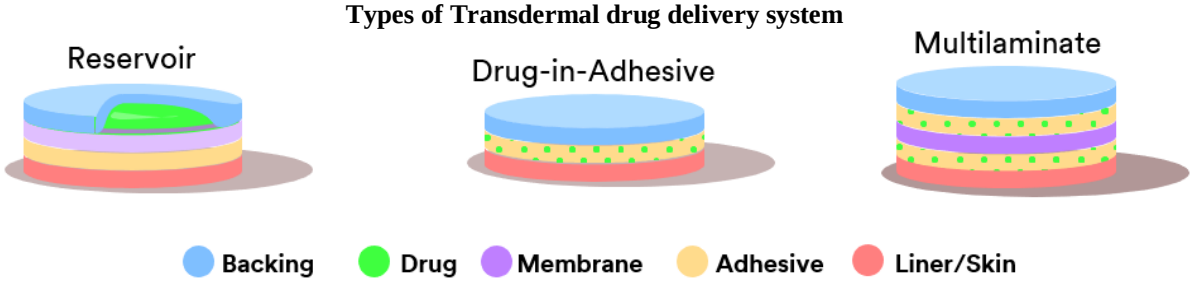

Figure-1: Designs of TDDS

A transdermal medication delivery system's backbone is polymers. A drug reservoir or a drug–polymer matrix is sandwiched between two polymeric layers: an outer impermeable backing layer that prevents drug loss through the backing surface and an inner polymeric layer that works as an adhesive and/or rate-controlling membrane in transdermal administration systems. The following three types of transdermal drug delivery systems can be generally classified.[R-3]

a) Reservoir system
b) Drug-in-Adhesive system
c) Multilaminate system

a) Reservoir system. The drug reservoir is sandwiched between an impermeable backing layer and a rate-controlling membrane in this device. Only the rate-controlling membrane, which might be microporous or nonporous, allows the drug to be released. The drug can be in the form of a solution, suspension, gel, or dispersed in a solid polymer matrix in the drug reservoir compartment. A small layer of drug-compatible, hypoallergenic adhesive polymer can be placed to the polymeric membrane's outside surface.

b) Drug-in-adhesive system. The drug reservoir is created by dispersing the drug in an adhesive polymer and then spreading the medicated polymer adhesive onto an impervious backing layer by solvent casting or melting the adhesive (in the case of hot-melt adhesives). Layers of unmedicated sticky polymer are put on top of the reservoir.

c) Multi laminate system.

Two medications are delivered at distinct times in this approach. In most cases, a bolus dosage is given first, followed by a maintenance dose.

Components of TDDS

A Transdermal Drug Delivery System majorly consists of the following components,

a) Adhesives
b) Backing membranes and Release liners
c) Active Pharmaceutical Ingredients
d) Additives
e) Plasticizers

a) Adhesives

Adhesive is the main component of the TDD and contributes to the various actions and some of the key parameters of adhesives which contributes to the performance of TDD are as mentioned below,

- Secure the system to the skin
- Contribute to the stability of the system
- Facilitate drug release from the skin
- Provide drug and excipient reservoir
- Biocompatible with the skin

There are various adhesive chemistries that are used in TDD system and some of the adhesives currently used in TDD are as follows

i. Acrylates
ii. Silicone
iii. Polyisobutylene

i. Acrylates

Pressure sensitive adhesives for use in transdermal patches must have as much contact with the skin's surface as feasible. To achieve this level of touch, the material must be able to bend under light pressure while yet overcoming the skin's roughness. When the patch is worn for an extended period of time, it has a liquid-like flow of PSA that results in wetting of the skin surface during the bonding phase and the capacity to resist shear and debonding pressures. The applicability of transdermal patches is dominated by interfacial adhesion and resistance to progressive debonding.[R-4]

A good PSA for a transdermal patch is non-sensitizing to the skin, has good initial and long-term adhesion properties to different skin phenotypes, is easy to remove without causing skin damage, leaves no residue on the skin after removal, is compatible with the API and excipients, and is comfortable to wear.[R-5,R-6] The following types of polymers comprise the majority of PSAs utilised since the commencement of transdermal patch development in the context of these requirements.

Adhesives made of acrylate Acrylic polymers are made by polymerizing alkyl esters of acrylic acid in an emulsion or organic solution[R-3] Figure-2 depicts the general structure of the group.

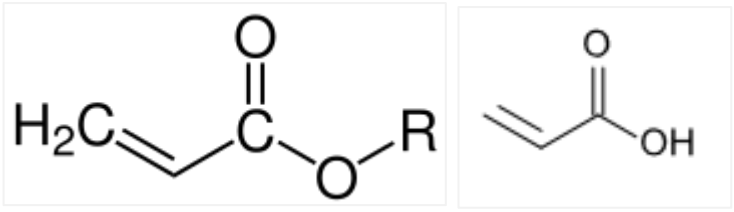

Figure-2: General chemical structure of Acrylate esters and Structure of Acrylic acid

R denotes an H-atom in an acrylic ester, –CH3 in a methacrylic ester, and R is an alkyl group usually in the C4–C8 range in a methacrylic ester. Acrylic homopolymers are poor adhesives by nature, as they have either good tack and low shear adhesion or good shear adhesion and low tack. As a result, copolymers must be designed using a combination of soft segments with a low homopolymer glass transition temperature Tg responsible for bonding (primary monomer) and hard segments with a higher homopolymer Tg responsible for debonding resistance (secondary monomer). A blend of different acrylic esters or the addition of vinyl monomers could be used to make such copolymers.[R-6, R-7.] Primary monomers are responsible for the tackiness and peel resistance of the product. The patent literature suggests using either n-butyl acrylate (BA) with a homopolymer Tg of -43 °C or 2-ethyl hexyl acrylate (EHA) with a homopolymer Tg of -58 °C as primary monomers with a PSA content of 50 to 98 percent by weight. Secondary monomers, also known as modifying monomers, are also required for a successful PSA, as previously stated. Methacrylate (MMA) and vinyl acetate (VAc) are two commonly employed monomers that give appropriate cohesive strength in the range of 10 to 35 percent by weight of the PSA.

They prevent cold flow, oozing, and dark rings by ensuring clean removal and resistance to shear pressures. Monomers having polar functional groups may be required in some circumstances to vary the number of dipole-dipole interactions due to adhesion adjustments or to change the polymer's pH. This may be necessary if the API or excipients behave as plasticizers, or if pH-sensitive medications require a specific environment. The solubility of the API in the polymer can also be altered by adding functional groups to the PSA. Carboxylic acids, such as acrylic or methacrylic acid, are commonly employed for this purpose. 2-hydroxyethyl acrylate is a desirable alternative monomer if acid-base reactions between the API and the polymer are predicted. It is normally utilised up to a fraction of 5% of the time. However, it has been found that amounts of up to 30% can boost API solubility. The storage modulus G' is exactly related to the molecular weight MW of acrylic PSAs.[R-8,R-9.]

ii. Silicone

[R-7,R-10,R-11]Silicone adhesives are made up of siloxane resins and linear silicone polymers. Polyorganosiloxanes are organosilicon polymers, with trimethylsiloxy-terminated polydimethylsiloxanes being the most common. (Refer Figure-3) High molecular weight silanol-functional silicone polymers and silanol-functional MQ siloxane resins make up silicone pressure sensitive adhesives (PSA). While a simple silicone polymer and resin mixture can provide an adhesive with appropriate peel adhesion and tack characteristics, it lacks sufficient cohesive strength. Silicone pressure sensitive adhesives are the result of a silanol condensation

reaction between the polymer and resin components, resulting in a network structure, and are generally referred to as standard pressure sensitive adhesives.[R-12]

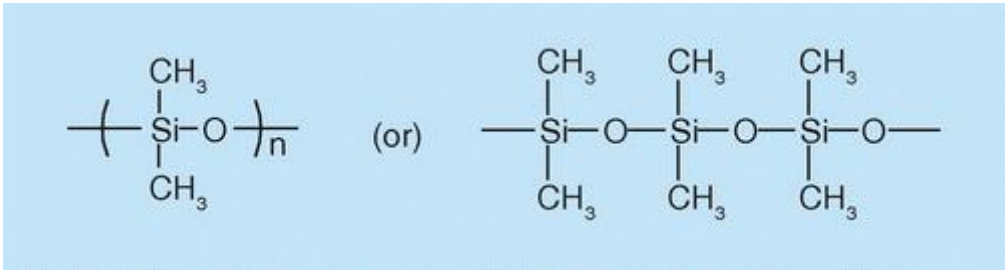

Figure-3: Chemical structure of Polydimethylsiloxanes

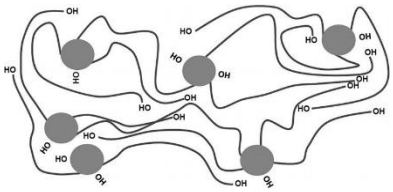

Figure-4: Schematic view of standard Silicone PSA

Multiple transdermal drug delivery system (TDDS) designs, including reservoir, matrix, and drug-in-adhesive (DIA) systems, have been documented in the literature and are commercially available; small variations and combinations of each of these patch designs can also be discovered.

iii. Polyisobutylene

PIB is a vinyl polymer produced by cationic polymerization from the monomer isobutylene (IB). PSAs based on PIBs are widely utilised in medicine, particularly for transdermal drug delivery (TDD) systems. Adhesives are employed in TDD applications to keep the patch in close contact with the skin surface. Because PIB polymer producers do not provide preformulated, ready-to-use adhesives, TDD patch makers or formulators must create their own PIB–PSA formulations.[R-13]

Adhesives made with polyisobutylene Since the early days of transdermal patch creation, polyisobutylenes (PIBs) have been employed as synthetic rubber adhesives. They're well-known in the tape industry, and they're made up of isobutylene homopolymers with a continuous hydrocarbon backbone and unsaturation only at the polymer chain ends. (See Figure-5). Transdermal patch makers must create their own PIB–PSA formulations by combining low and high molecular weight PIBs to achieve a balance of tack and cohesive strength because PIB polymers are not available as ready-to-use adhesives.[R-14.] Ready-to-use PIBs have a strong initial tack, great skin peel resistance, and are relatively affordable. PIBs are still good adhesive choices for transdermal patches because of their stability, inertness, and widespread acceptance in FDA-regulated applications. The main drawbacks of PIB adhesives are their lack of long-term cohesiveness at skin temperature. Another disadvantage is their limited permeability to air and water vapour. On one hand, occlusion may be desirable in order to improve medication flow through the skin. Skin maceration and irritation, on the other hand, are possible side effects, especially if the patch is left in the same position for an long period of time.

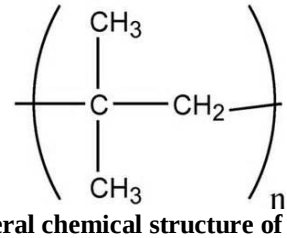

Figure-5: General chemical structure of Polyisobutylene

b) Backing membranes and release liners

i. Backing layer

When creating a backing layer, the developer must prioritise the material's chemical resistance. Excipient compatibility must also be taken into account because prolonged interaction between the backing layer and the excipients might cause additives to leach out of the backing layer or excipients, drugs, or penetration enhancers to diffuse through the layer. However, putting too much focus on chemical resistance can

lead to stiffness and excessive occlusivity to moisture vapour and air, which can cause patches to lift and irritate the skin over time.[R-15]. A patch was created with a revolutionary alteration to the traditional design in which the backing itself served as a drug reservoir. After being applied, the top internal section of the drug reservoir penetrated the porous backing and solidified inside, bringing the reservoir and the backing together. This change allowed the backing to serve as a storage site for the medication-filled reservoir.[R-16]

The backing membrane is a crucial component of the transdermal drug delivery system. It shields the matrix from the outside environment and is chosen based on appearance, flexibility, and the necessity for occlusion.[R-17]. The backing membrane material should be inert and incapable of absorbing medications or other formulation ingredients. Polyesters, polyethylene, polypropylene, and polyurethane are examples of polymers that can be used for the backing.[R-18.] The backing membrane's thickness should be between 15 and 250 mm, and it can be coloured or vapour coated with aluminium. With the preservation of moisture vapour and air, metal layers often contribute to stiffness and high occlusiveness, causing the transdermal patch to tear off and perhaps irritate the skin over time. The backings are tan or translucent, with a matte surface that is usually writable. Because of the potential for reactive by-products to develop during the Corona treatment, it is not used in backing membranes for pharmaceutical applications.

ii. Release liner

A protective liner covers the patch during storage, which is removed and discharged just before the patch is applied to the skin. As a result, it is considered a component of the principal packing material rather than a component of the dosage form that delivers the active ingredient [R-19]**.** However, because the liner comes into direct contact with the delivery system, it must meet certain standards for chemical inertness and drug, penetration enhancer, and water permeation. If cross-linking between the adhesive and the release liner occurs, the force necessary to remove the liner will be excessive.[R-20.] The liner thickness must be precise in order to allow die cutting, and is normally between 50 and 150 m. For example, 3M company manufactures release liners made of fluoro polymers (Scotchpak 1022 and Scotchpak 9742, 3M Drug Delivery Systems, St. Paul, MN)

c) Active pharmaceutical ingredients

A transdermal patch typically contains enough API to maintain therapeutic blood levels for up to seven days. To get a high API flow through the skin, the API should be dissolved in the matrix close to its solubility limit, but not much beyond it. There is a substantial danger of API recrystallization during storage in supersaturated conditions.[R-21.]

The following are some of the desirable properties of a drug for transdermal delivery.
Ideal Properties of Drug for Transdermal Drug Delivery[R-22 & R-23]

- Dose Less than 20mg/day
- Half-life < 10 hrs
- Molecular weight < 400 Daltons
- Melting point < 200°C
- Partition coefficient 1 to 4
- Skin permeability coefficient > 0.5×10^{-3} cm/hr
- Skin reaction non irritating and non sensitizing
- Oral bioavailability Low

d) Additives/Penetration enhancers

Because of the strong barrier qualities of the SC, penetration enhancers accelerate the permeability of a medication across the skin (the uppermost layer of the skin). Although some lipophilic solvents and surface-active compounds have been proven to be excellent penetration enhancers, their irritability and sensitivity limit their use. A novel form of polymeric enhancer that permeated through the skin was described by Aoyagi et al. (1990, 1991).[R-24]

[R-23]These are the compounds that increase skin permeability by changing the skin's function as a barrier to the flux of a desired penetrant, and they're found in almost all transdermal formulations. The resistance of skin to drug diffusion must be lowered in order for drug molecules to pass skin and therapeutic levels in blood to be achieved and maintained. They have the ability to alter the skin's barrier to penetration by reacting with the formulation or the skin itself. (Jalwal et. al. 2010)

e) Plasticizers:

Plasticizers are non-volatile organic liquids or solids with a low melting point that alter the physical and mechanical properties of polymers when added.[R-25]

Plasticizers are generally utilised in the proportions of 5-20% in transdermal therapeutic systems, according to research. Figure-6 shows the chemical formulae of six plasticizers commonly utilised in transdermal drug delivery experiments.

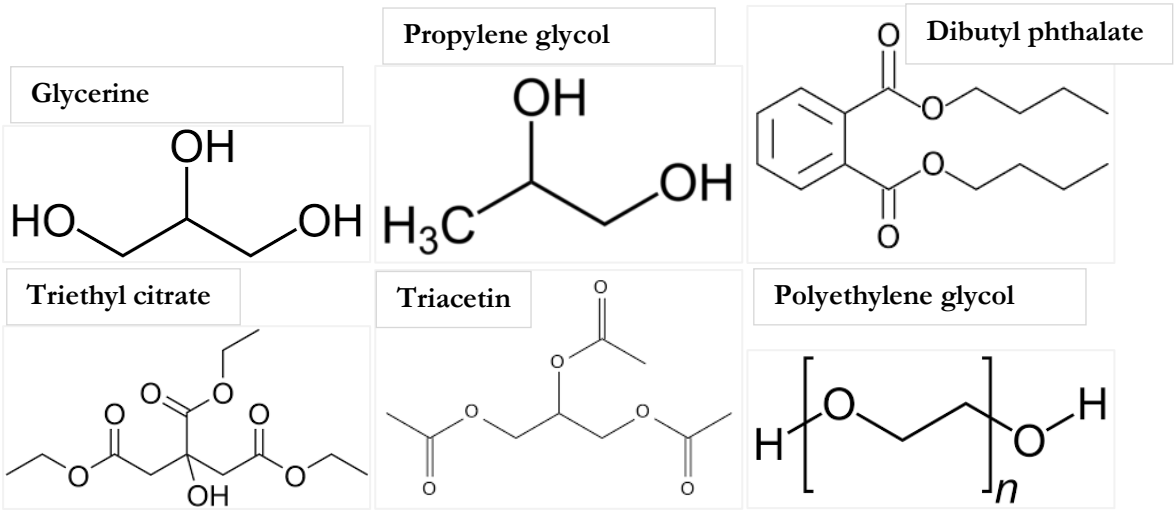

Figure-6.: Chemical formulas of plasticizers frequently used in transdermal drug delivery studies

Plasticizers including phthalate and citrate esters, as well as glycol derivatives, are frequently used in transdermal film manufacture (Gal & Nussinovitch, 2009). In the table below, the plasticizers utilised in the study, their amounts, and the polymers with which they were used are stated. (Table-1).

The following are some of the reasons why plasticizers should be added to polymer films used in transdermal medication delivery systems:

• Reducing the brittleness • Improving flow • Ensuring flexibility • Enhancing the resistance and tear strength of the polymer film (Bergo & Sobral, 2007; Felton, 2007; Rao & Diwan, 1997).

Table-1. The plasticizers used in the transdermal patches with their proportions and polymers

Base Polymer	Plasticizer (% w/w)	Transdermal system type	Reference
Cellulose acetate	Dibutyl phthalate Propylene glycol Polyethylene glycol 600 (40%)	Drug free film	Rao & Diwan, 1997
Polyvinyl Alcohol 72000	Glycerine (4%)	Matrix	Padula et al., 2003
Carboxymethyl Guar	Polyethylene glycol 400 (40%)	Matrix	Murthy et al., 2004
Ethyl cellulose: Polyvinylpyrrolidone Eudragit: Polyvinylpyrrolidone	Dibutyl phthalate (20%)	Matrix	Mukherjee et al., 2005
Polyvinyl Alcohol	70% Sorbitol Solution (2%)	Matrix	Nicoli et al., 2005
Hydroxypropyl cellulose Eudragit RL PO Silicon Gum Acrylate copolymer	Triethyl citrate (6%)	Film forming polymeric solution	Schroeder et al., 2007
Pectin	Propylene glycol (10%)	Matrix	Güngör et al., 2008
Hydroxypropyl methyl cellulose E15: Eudragit RS 100 Hydroxypropyl methyl cellulose E15: Eudragit RL 100	Propylene Glycol (15%)	Matrix	Karunakar et al., 2010
Eudragit E100 Polyvinylpyrrolidone	Dibutyl phthalate (5%) Dibutilsebacate (10%)	Matrix	Rajabalaya et al., 2010
Hydroxypropyl methyl cellulose, Eudragit RL 100, Chitosan	Triethyl citrate (5%)	Matrix	Shinde et al., 2010
Polyvinyl Alcohol Polyvinylpyrrolidone Trimethoxy silane	Glycerine (10%)	Matrix	Guo et al., 2011

When it comes to optimising a transdermal drug delivery system, there are various factors to consider. In transdermal systems, the choice and design of polymers, adhesives, penetration enhancers, and plasticizers

are critical for drug release characteristics as well as the formulation's mechanical qualities. Plasticizers, in addition to the other components of transdermal patches, have a substantial impact on the viscoelastic properties of the polymers. Plasticizers are used in transdermal drug delivery systems for a variety of reasons, including improving film forming characteristics and appearance, reducing film cracking, enhancing film flexibility, and achieving desired mechanical qualities. As a result, great consideration should be given to the plasticizer type as well as the concentration of the plasticizer in the formulation.[R-26]

IV. Description and Advantages of Transdermal Drug delivery system

[R-24] For an effective and optimal treatment response, medication selection and an effective drug delivery system (DDS) are critical. There are numerous routes of administration, with the oral route being the most popular for drug delivery due to substantial benefits such as ease of administration and others. However, this approach has a number of disadvantages, including poor bioavailability due to first-pass metabolism of some medications, as well as a tendency to generate fluctuations in plasma drug concentration, necessitating frequent dosing, which is inconvenient and costly for the patient. To overcome the challenges of the oral route, innovative DDS are needed, which can improve the therapeutic efficacy and safety of medications while also lowering the dose and dosing frequency. The development of transdermal delivery systems (TDDSs) is one of the most inventive and effective fields of drug delivery research, as it addresses some of the constraints of standard dosage forms. The human skin is an easily accessible surface for drug administration and effective transdermal drug delivery (TDD); however, the drug must be able to permeate the skin barrier in order to reach the target site. TDD differs from topical drug delivery in that it delivers the medicine into the systemic circulation at a predetermined and regulated rate, whereas topical drug delivery focuses on localised locations. The type of dosage form and the extent of drug absorption at the site of administration determine the medication's concentration at the site of action, which is responsible for both the desired therapeutic impact and any unwanted side effects. According to statistics, the TDDS market was worth $12.7 billion in 2005, $21.5 billion in 2010, $37.79 billion in 2018, and $49.37 billion in 2024. Some of the marketed transdermal products with their indication and duration of action are given in Table-2

Table-2: Transdermal product List

Name of Drug	Name of Product	System	Duration of action	Manufacturer	Indication
Alora	Estradiol	Matrix	3 to 4 days	TheraTech/Procter & Gamble	HRT for PMS
Androderm	Testosterone	Membrane	24 h	TheraTech/GlaxoSmithKline	Hypogonadism in males
Catapres-TTS	Clonidine	Membrane	7 days	Alza/Boehringer-Ingelheim	Hypertension
Climara	Estradiol	Matrix	7 days	3M Pharmaceutical/Berlex Labs	PMS
CombiPatch	Estradiol/ norethindrone	Matrix	34 days	Noven Inc./Aventis	HRT
Duragesic	Fentanyl	Membrane	72 h	Alza/Janssen Pharmaceuticals	Moderate/ severe pain
Deponit	Nitroglycerin	Drug in adhesive	10 to 12 hrs	Schwarz-Pharma	Angina pectoris
Estraderm	Estradiol	Membrane	3 to 4 days	Alza/Novartis	PMS
Esclim	Estradiol	Matrix	34 days	Women First HealthCare	PMS
Habitrol	Nicotine	Drug in adhesive	24 h	DR Reddys Labs SA	Smoking Cessation
Matrifen	Fentanyl	Reservoir	3 days	Takeda UK Ltd	Pain relief
Minitran	Nitroglycerin	Matrix	12 to 16 hrs	3M Pharmaceuticals	Angina pectoris
NicoDerm	Nicotine	Membrane	24 hrs	Alza/GlaxoSmithKline	Smoking cessation
Nitrodisc	Nitroglycerin	Matrix	24 h	Roberts Pharmaceuticals	Angina pectoris
Nicotrol	Nicotine	Matrix	16 hrs	Cygnus Inc/McNeil Consumer Products Ltd	Smoking cessation
Nitro-Dur	Nitroglycerin	Matrix	12 to 16 hrs	Merck, Bayer Schering Pharma	Angina pectoris
Ortho Evra	Norelgestromin/ ethinyl estradiol	Matrix	7 days	anssen Pharmaceuticals, Inc., Ortho-McNeil and Evra	Contraceptive
Testoderm	Testosterone	Membrane	24 hrs	Alza	Hypogonadism in males
Transderm Nitro	Nitroglycerin	Membrane	12 to 16 hrs	Alza, Novartis	Angina pectoris
Transderm Scop	Scopolamine	Membrane	72 hrs	Novartis	Motion sickness

Vivelle	Estradiol	Matrix	3 to 4 days	Novartis	Hormone therapy
Vivelle-Dot	Estradiol	Matrix	3 to 4 days	Novartis	Hormone therapy

4.1 Advantages of drug delivery via transdermal route

TDD has a variety of advantages compared to other routes some of which are as follows:

• A relatively large and readily accessible surface area (12 m^2) of the skin for absorption (Naik et al., 2000)
Termination of drug therapy is easy at any point of time, either systemic or local (Patel et al., 2011).

• Avoidance of first-pass metabolism, that is, in the liver and gastrointestinal tract drug is protected from being degraded and other factors associated with the gastrointestinal tract such as pH, gastric emptying time (Naik et al., 2000; Shah and Maibach, 1993; Henzl and Loomba, 2003; Kornick et al., 2003).

• The drug having shorter biological half-lives and a narrow therapeutic window have an advantage of sustained release of the drug via the transdermal route (Naik et al., 2000; Varvel et al., 1989; Yang et al., 2004).

• Minimization of undesirable side effects associated with systemic toxicity (Patel et al., 2011; Kornick et al., 2003; Cramer and Saks, 1994)

4.2 Drug absorption mechanism in Transdermal drug delivery system

The function of the skin is a key obstacle to medication distribution via transdermal method. Erythema, local irritation, edoema, discomfort, itching, and inflammation are all side effects of TDDS caused by the medicine and other substances. Initially, skin served as an impenetrable barrier, but subsequent research and analysis on the skin demonstrated its utility as a route for systemic delivery. "A slower diffusion of drug from the TDDS is driven by the gradient between the greater concentration in the delivery system and the zero-concentration prevailing in the skin," says the principal mechanism for drug delivery. Drug molecules from the TDDS can enter the skin in three ways: (1) by sweat ducts, (2) through the follicular region via hair follicles and sebaceous glands (i.e., shunt or appendageal route), and (3) through the unbroken SC between the appendages. **R-24.**

Transdermal permeation is affected by physicochemical factors of the Drug Delivery System, such as release characteristics, DDS composition, and the presence of a penetration enhancer, which are detailed next (Tyle, 1998).

The amount of drug solubilized in the vehicle determines the drug release rate. The drug release mechanism is determined by several parameters, including whether the drug molecules are suspended or dissolved in the formulation, the drug's partition coefficient (interfacial) from the formulation to the skin, and the formulation vehicle's pH. The medication delivery systems' composition, The DDS's composition, such as boundary layers, thickness, polymers, and carriers, influences not only the drug's release rate but also its permeability into the Stratum corneum. Enhancer of drug permeability The majority of medications do not enter the skin at a sufficient pace to be therapeutically effective. Permeation enhancers, such as organic solvents [dimethyl sulfoxide, dimethylacetamide, dimethylformamide, ethylene glycol, and polyethylene glycol (PEG)], surface-active agents (sodium lauryl sulphate, sodium dioctylsulfosuccinate), azones (laurocapram), and others, are added to the DDS to improve drug transdermal permeation.

Typical Evaluation parameters of Transdermal Products

By delivering a lower amount of medicine at a predefined rate, transdermal patches have been designed to increase clinical efficacy and patient compliance. This emphasises the importance of evaluation studies to guarantee that the intended performance and reproducibility are achieved under the defined environmental circumstances (Bhavna Yadav et al., 2011). These studies forecast transdermal dose formulations and are divided into the following categories:

a) Evaluation of adhesive
b) Physicochemical evaluation
c) In vitro drug release evaluation
d) In vivo evaluation
e) Cutaneous toxicological evaluations

a) Evaluation of adhesive

Pressure sensitive adhesives are evaluated for the following properties (Jain N. K., 2004)

1) Peel adhesion properties
2) Tack properties
- Thumb tack test
- Rolling ball tack test

- Quick stick test (peel tack test)
- Probe tack test

3) Shear strength properties

1) Peel adhesion test:

The force required to remove an adhesive coating from a substrate is referred to as peel adhesion. A single tape is put to a stainless-steel plate, then the tape is pulled away from the substrate at an angle of 180°, and the force it takes to pull the tape is measured.

2) Tack properties:

Thumb tack test: This test assesses the adhesive's tackiness. The tack property is determined by pressing the thumb on the adhesive.

Rolling ball tack test: This test detects the tackiness of the polymer by determining the softness of the polymer. The 7/16-inch-diameter stainless-steel ball is launched on an inclined track, rolling down and making contact with horizontal, upward-facing adhesive. Tack is measured in inches by the distance travelled by the ball along the adhesive track.

Quick stick (Peel-tack) test: Peel force is determined by pulling the force away from the substrate at 90° at a speed of 12 inch/min to break the bond between the adhesive and the substrate.

Probe tack test: The probe with the specific surface was placed in contact with the adhesive to make a bond. The probe is then removed, mechanically breaking it. The tack is the force necessary to pull the probe, which is measured in grams.

3) Shear strength properties: The cohesive strength of an adhesive polymer is measured which relates to shear strength. When a device's cohesive strength is adequate, it won't slip on application and won't leave any residue when removed. It's calculated by timing how long it takes to remove adhesive-coated tape off a stainless-steel plate when a specific weight is suspended from the tape, pulling the tape in a parallel to the plate direction.

b) Physicochemical evaluation

R-27, R-28, R-29, R-30 and R-23 Physical Appearance • Weight variation • Thickness of the patch • Folding Endurance • Flatness • Percentage Moisture Content • Estimation of drug content

i. Thickness of the patch: The thickness of the patch is measured using a digital micrometre at several spots to establish the average thickness and standard deviation.

ii. Weight of uniformity: The patch is dried for 4 hours at 60 degrees Celsius before being tested. That patch was cut into several pieces and weighed in a digital balance. Take the average weight and divide it by the individual weight to get the standard deviation.

iii. Folding endurance: A section of strip is sliced and folded repeatedly in the same spot until it breaks. The value of folding endurance was determined by the number of times the film could be folded without breaking.

iv. Percentage moisture content: The produced patches must be weighed individually and stored at room temperature in a desiccator containing fused calcium chloride. The films must be reweighed after 24 hours and the percentage moisture content calculated using the formula below:

Percentage moisture content (%) = [Initial weight - Final weight / Final weight] ×100 f)

v. Percentage moisture uptake: To maintain an 84 percent Relative humidity, the produced patches must be weighed individually and stored in a desiccator with a saturated potassium chloride solution (84%RH). The films must be reweighed after 24 hours and the percentage moisture uptake calculated using the formula: Percentage moisture uptake (%) = (Final weight - Initial weight / initial weight) × 100 g)

vi. Determination of surface pH: A certain number of patches are kept in contact with distilled water, the excess water is drained, and the pH of the water is measured using a pH metre.

vii. Flatness test: From various parts of the films, three longitudinal strips are cut. The length of each strip is measured, as well as the variation in length due to non-uniformity in flatness, using the percentage constriction method, with 0% constriction equalling 100% flatness.

viii. Percentage elongation break test: The following formula can be used to calculate percentage elongation: L1-L2*100/L2 elongation percentage Where L1 is the strip's end length and L2 is the strip's initial length.

ix. Folding Endurance: Folding endurance testing entails assessing the folding ability of films that have been subjected to repeated harsh folding circumstances. Folding endurance is measured by folding the film in the same spot over and over until it breaks. Folding endurance value is the number of times a film can be folded in the same spot without breaking.

x. Tensile Strength: The film is pulled at specific rate (mm/min) on a tensile testing machine, and the strength when the film sample tears (a value determined by dividing the tensile load by the cross-sectional area of the sample) and the amount of elongation are calculated.

xi. Drug content: Dissolve the patch with a given area in a specific amount of solvent. The solution is subsequently filtered, and the drug content is determined using the appropriate procedure (UV or HPLC technique). Then add up three distinct samples to get an average.

xii. Uniformity of dosage unit test: Take ten patches and determine the content for each one. Transdermal patches pass the content uniformity test if 9 out of 10 patches have content between 85 and 115 percent of the given value and one patch has content between 75 and 125 percent of the required value. If the composition of three patches is between 75 and 125 percent, an additional 20 patches are tested for drug content. If the results of these 20 patches range from 85 to 115 percent, the transdermal patches have passed the test.

c) Invitro Drug release evaluation

[R-31, R-32]One of the most critical studies for all controlled release delivery systems is the release rate determination. Patch dissolution studies are important because, to establish a constant rate of drug permeation, the drug concentration on the stratum corneum's surface must be consistent and significantly greater than the drug concentration in the body. The dissolution investigation was conducted out utilising a USP Paddle Type Dissolution Apparatus at 32±10°C with a paddle rotation frequency of 50 rpm. The dissolution media was 500 mL of MIPB with a pH of 7.4. The patches were then placed in a jar and fastened with a fine copper wire. Samples were taken at various intervals and compared to a blank using a UV Spectrophotometer set to 238 nm. The formula was used to calculate the percentage of medication released: % of drug released = Da/Dt × 100 ---------- Where, Dt **—** indicates the total amount of drug in the patch and Da — the amount of drug released.

Pharmacokinetic assessment of Drug absorption of Transdermal patches

There are numerous methods for analysing drug penetration into the skin, which is a key metric for assessing the performance of TDDS. The following approaches can be used to examine the pharmacokinetics of a topically applied product or TDDS.

d) Invitro Skin permeation study or Ex vivo skin permeation study

Drug released from polymeric transdermal films has a significant impact on the amount of drug available for absorption into the systemic pool. The medication reaches the dermal microcirculation by passing between epidermal cells and between epidermal cells via skin appendages.

Various skin models that have been utilised by different researchers. Although there is no set rule for choosing a skin model. However, most studies begin with an artificial membrane, then move on to in vitro animal skin, in vitro human skin (cadaver skin), in vivo animal skin, and lastly in vivo human skin. [R-31, 32].

Ex vivo penetration and permeation studies of medicines and other substances are commonly conducted to determine percutaneous absorption and transdermal permeation characteristics. This ex vivo experiments allow for the measurement of drug concentration in the skin (penetration) as well as the rate of drug transfer across the skin (permeation). Ex vivo experiments are simple to conduct, and the methodology's simplicity allows for customising the model to many aspects of preliminary or feasibility studies in the development of skin/transdermal drug delivery systems. Human corpse skin would be preferable for in vitro permeation investigations, however in fact, human cadaver skin is not readily available for most investigators. As a result, animal skin is commonly employed in in vitro research. In terms of permeability and lipid composition, weanling pig skin (skin from a recently weaned pig) is considered the closest substitute for human cadaver skin.

Hairless guinea pigs and Brattleboro rats tend to be good animal models for skin/transdermal drug delivery systems; however, snakes do not appear to be a useful model for evaluating drug permeability over skin. When examining research comparing transdermal medication absorption in animals and humans, extreme caution must be exercised to determine the effects of technique and model on the findings, as well as to avoid any misinterpretation or incorrect conclusions. According to the research, there is no consensus on animal models that accurately mirror human skin. Preparing the Skin, the animals' skin was removed in the appropriate places. Fat, tissue, blood vessels, and epidermal hairs were meticulously removed from beneath the skin. The skin was washed with regular saline and then sterile water if there were no evident holes or abnormalities. It was then chilled for 12 hours after soaking in phosphate buffer pH 7.4 solutions. The skin was thawed at room temperature and utilised to perform ex-vivo skin permeation[R-33,R-34.]

Drug concentration in the skin, penetration, velocity of drug transport through the skin, and permeation can all be detected using in vitro and ex vivo experiments. The Franz diffusion cells method is extensively used in ex vivo skin permeation experiments.

Franz cell is a multipurpose blown glass diffusion cell with a donor chamber open to the air and a stirred receptor chamber that is commonly used in the development of transdermal applications. Below are some of the main components of Franz diffusion cell.

Franz diffusion cell components:

i) Membrane - any biological or manmade layer of material.
ii) Diffusion Cell - a donor chamber, receptor chamber, membrane, and cell clamp to hold the assembly together
iii) Donor Chamber - the part of a diffusion cell, where the compound of interest, is placed at the beginning of a study

iv) Receptor Chamber - the part of a diffusion cell, into which particles of the compound of interest may migrate
v) Joint - the interface between the donor chamber and receptor chamber, or the interface surface of each chamber
vi) Orifice - the hole in the joint surface of either the donor or receptor chamber, usually the receptor chamber, the same hole covered by the membrane
Orifice Diameter - the diameter, in metric units and usually millimetres, of the orifice - the orifice diameter is how diffusion cell size is specified. A 9mm Franz Cell has a 9mm orifice diameter. A 15mm Side-by-Side Cell has a 15mm orifice diameter.
Orifice Area - the area of the orifice in centimetres, which is important to know for diffusion calculations
vii) Receptor Volume - the volume of the receptor chamber in millilitres, which is important to know for diffusion calculations
viii) Sampling Arm - a port through which a device is inserted, to withdraw receptor fluid from the receptor chamber. Some unjacketed Franz Cells have large diameter sampling arms for pouring out all the receptor fluid for analysis, instead of just removing a sample. These are called dump cells.

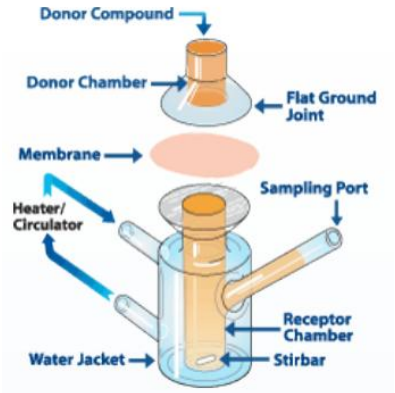

Figure-7: Jacketed Franz cell with Flat ground joint.

Other important considerations for Intravenous permeation test:
i) Membrane Types
There are several types membrane system was used for the Franz diffusion study cell and below are some of them which needs more attention,
a) Human tissue ex vivo: It may be challenging to get adequate quantities of normal, healthy human tissue for statistical analysis of permeability tests with large sample sizes. Many laboratories use human cadaver skin from accredited human tissue banks in the United States. Obtaining human tissue biopsies and surgical specimens may raise ethical and legal concerns.
b) Small animals: Rats, mice, and rabbits have long been utilised in studies of human tissue permeability because they are relatively inexpensive to buy and keep. The tissue portions are typically thinner and have a different shape than human skin, resulting in larger compound permeabilities.
c) Large animals: Monkeys, dogs, pigs, and other large animals have also been employed frequently, but they can be costly to acquire, especially monkeys and dogs. Because pig and monkey soft tissue has a form and function that is remarkably similar to human soft tissue, it is frequently utilised as a substitute for human skin.
d) Polymeric membranes: In vitro release testing is the most common application for these membranes (IVRT). SUPAC-polymeric membranes with a pore size of 0.45 m are utilised, according to "FDA Guidance for Industry: Nonsterile Semisolid Dosage Forms: Scale-Up and Post approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation, May 1997." The same membrane should be utilised for the course of the project once it has been set during the IVRT technique development phase.
e) Human skin equivalents (HSEs): These are tissue-engineered 3D skin constructs (such as MatTek products) that combine cultivated human skin cells with extracellular matrix components in a controlled culture environment. The benefit of these tissues is that their vitality can be preserved. The key disadvantage is that the simulated tissue's permeability is often higher than in vivo.
ii) Donor Formulations:
Liquid solutions, suspensions, creams, gels, ointments, lotions, pastes, powders, or adhesive patches are all possible forms for the molecule of interest. The chosen formulation should be as close to the real-world application as possible. Changing the formulation, concentration, and adding permeability enhancers can all help you learn more about the permeant's properties and behaviour.

iii) Receptor Media:
The nature of the permeant and the type of diffusion cell used determine the receptor solution. In vitro permeability experiments require a receptor media that closely resembles the in vivo scenario. Because flow-thru systems reduce the amount of build-up in the receptor chamber, watery receptor fluid is usually sufficient. This could be a problem in static cells when the permeant isn't cleansed on a regular basis.
iv) Sampling:
Your study topic will determine the optimum technique of sampling in terms of time intervals, frequency, and volume, as well as the best method of reporting the permeation of a compound of interest. Do you want to know how much compound crosses a membrane at short intervals, how much compound crosses the membrane over a long sampling period, or how much compound is found within the membrane after a specific exposure period? Do you need to figure out flow, accumulation, or the permeability constant? (Kp).
v) Flux and Permeability coefficient:
Calculating Flux and Permeability Coefficient (KP): Flux (J) is the amount of permeant crossing the membrane per time. It is given in units of mass/area/ time or in units of radioactivity/area/time. Note: If the permeant was applied in a finite dose, then you can only calculate a flux by the formula: $J = Q /(A \bullet t)$ where Q is the quantity of compound traversing the membrane in time t, and A is the area of exposed membrane in cm2. Units of flux are quantity/cm2/min

e) In vivo evaluation

The in vivo approach relies on a system that is physiologically and metabolically intact. In vivo investigations can be divided into two categories.[R-35,R-34]
1) Animal studies 2) Human studies

1) Animal studies:

Because human research takes a long time and demand a lot of resources, in vivo animal models are chosen. Some of the species that have been used for in vivo testing include mouse, rat, guinea pig, rabbit, hairless mouse, hairless rat, hair less dog, cat, dog, pig, swine, horse, goat, squirrel, monkey, rhesus monkey, chimpanzee, etc. Various experiments have been carried out to determine which of the animal models provide the best prediction of the behaviour of the device, being tested, in humans. The most frequently used animal is the rat even though it is well known that rat studies generally overestimate human skin absorption. Other animals, such as the Rhesus monkey, are more dependable in vivo models and have a greater agreement with human absorption, but their expenses are significantly higher. Hairless animals are favoured over hairy animals in both in vitro and in vivo trials, according to the results of many experiments. Percutaneous absorption was studied by a group of researchers, who discovered a decreasing sequence of permeation: rabbit>rat> swine>man. Other studies, however, have demonstrated that data from these lesser animals is equivalent to that of humans, despite the fact that animal studies, whether in vivo or in vitro, can only be useful approximations of human behaviour.[R-36.]
In vivo investigations were conducted on Wistar albino male rats weighing 200-220 g. The animals were obtained from the Innovative Institute of Pharmacy's animal house in Greater Noida, Uttar Pradesh (Registration number: 1346/PO/Re/S/10/CPCSEA dated 16/06/17). The Institutional Animals Ethics Committee gave their blessing to the research. The rats were kept in conventional lab conditions, which included 24-26 degrees Celsius, 50 to 60 percent relative humidity, and a 12-hour light/dark cycle. The rats were housed in stainless steel cages with free access to food and water. A superficial inspection of the surface skin for anomalies was used to select the rats. The dorsal side of the rats was cut to roughly 6 cm2. The rats were starved for the duration of the study (24 hours) to see if shaving had any negative effects. Using a lateral tail vein approach, plasma samples were taken at different intervals of time, i.e. 2, 4, 8, and 24 hours. Plasma samples were centrifuged (Remi, RM-12C, microcentrifuge) and stored at -70 oC in Eppendorf tubes. The drug concentration in plasma was determined in the Reverse Phase using a validated High-Performance Liquid Chromatography (RP-HPLC) method.[R-37]
Microdialysis: Microdialysis probes were implanted into two places in the epidermis and bilateral knee joints of rats to determine drug concentrations. Perfusion of the probe began at a flow rate of 1.2 L/min with PBS, and insertion trauma was allowed to diminish for 60 minutes. Patches containing ketoprofen 0.51 mg per 2.4 cm2 (0.83 cm) were placed to the one side of the skin and knee joint where the microdialysis probe was implanted after a 60-minute baseline dialysate sample. Each of the remaining points was a non-application location. The dialysis solution was then sampled every 60 minutes for up to 480 minutes following administration. The carotid artery catheter was used to collect plasma. Microdialysis probes were placed into two sites in the skin and bilateral knee joints of pigs to determine drug and prostaglandin E2 concentrations, as shown in Fig. 1B. Perfusion of the skin and knee joint with PBS was initiated at a flow rate of 1.5 L/min, and insertion trauma was allowed to diminish for 60 minutes. Patches containing ketoprofen 7.5 mg per 35 cm2 (7 5 cm) were applied to one side of the skin and knee joint where the microdialysis probes were inserted after 60 minutes of baseline dialysate collection. Every other location was a non-drug application site. The dialysis solution was then

sampled every 60 minutes for up to 480 minutes following administration. A central venous catheter was used to collect plasma. Unbound fractions were used to quantify ketoprofen concentrations in dialysate, and total bound and unbound fractions were used to estimate ketoprofen concentrations in plasma. All samples were kept at 40°C until ketoprofen and prostaglandin E2 levels were determined.[R-38]

2) Human studies

The in vivo clinical investigations on humans are the final phase of a drug's transdermal absorption studies. The standard principals mentioned were applying the test substance to the skin in the proper form and time, taking samples of various body fluids, excreta, or tissue at certain intervals, and measuring the test substance or metabolite in the samples using a sensitive analytical method. The use of volunteers in in vivo investigations is strictly restricted. An ethics committee must approve the study protocol, and the subjects must provide written informed permission.

In vivo percutaneous research can be done using a variety of approaches. The following are some of them:

i. Traditional in vivo technique (Plasma/ excreta measurement)

Blood and/or urine are taken and analysed after the test chemical is applied to the skin of healthy persons. The amount of test substance detected in the blood and/or urine is a good indicator of the amount absorbed into the systemic circulation through the skin. In vivo tests, the chemical is applied to a specific area of the skin site of volunteers/animals for a set period of time. Analysing the parent chemical and/or its metabolite(s) in the skin layers or biological media such as plasma, urine, or exhaled air can be used to determine percutaneous absorption. After cutaneous exposure, the amount of a chemical detected is compared to the amount measured after a reference exposure with a defined dose, such as intravenous administration or inhalation. This in vivo technique was utilised before all other procedures were investigated, and it is currently employed in situations when the volunteers are not at risk. Often, a substance's test is designed to reveal several unknown features of the material, implying that understanding of the substance is limited or partial, and so the risk assessment may be incomplete. This raises ethical issues and restricts the utilisation of healthy volunteers. [R-39].

ii. Microdialysis

Microdialysis is a technique for sampling endogenous and exogenous chemicals in the extracellular space of living tissue, such as the skin, that is utilised in both clinical and research settings. Microdialysis is the only technology that currently delivers information from the extracellular space, making it crucial in the study of pharmacological and biochemical procedures in these tissues. Even though most medications have an effect in the tissues rather than the bloodstream, serum concentrations of different compounds are used to determine a variety of findings in drug discovery and development. As a result, data on pharmacokinetics at the target location are crucial, just as determining pharmacodynamic effects in relation to tissue drug concentrations in the target tissue is a more exact way of describing exposure effects. Microdialysis is the most important instrument for estimating active drug profiles at the target location, as well as giving pharmacokinetic and pharmacodynamic data. Microdialysis is based on the idea of simulating the function of a small blood artery in the dermis. A skin test material will penetrate the epidermis to the dermis, where the fake blood vessel/probe will be implanted. The probes have a semipermeable construction that allows molecules to passively diffuse into the perfusate inside the probe. As the perfusate inside the probe flows through at a steady and extremely precise rate, the molecules follow a concentration gradient across the probe membrane. Molecules are partially equilibrated across the membrane. The perfusate, now referred to as the dialysate, exits the probe, carries the test chemical, and is collected in small vials for examination. This method has been utilised on both human and animal volunteers.[R-40].

iii. Tape stripping method

Tape stripping is a common in-vivo procedure that can also be employed in vitro. A test substance (typically radioactively labelled) is permitted to penetrate the skin for a specific amount of time in a predetermined location. The skin is then gently cleansed to eliminate any residual unabsorbed test substance on the surface. The process next entails repeatedly applying and removing adhesive tape to remove microscopic layers of the exposed stratum corneum. The levels of recovered material in these tape-attached shredded cells are next analysed using a suitable analytical method. The amount of chemical in these skin layers was discovered to be an excellent predictor of the overall amount of chemical absorbed into the systemic circulation. Because only dead cells (corneocytes) buried in their lipid matrix are removed, the process is affordable, simple, and minimally intrusive. Tape stripping is especially useful for determining the local bioavailability of medications whose target site is the stratum corneum itself, such as antiseptics and antifungal agents.[R-41].

V. Other Analytical studies

5.1 Drug and PSA (adhesive) Interaction studies

[R-42]Drug and Adhesive interaction study is very important parameter to select appropriate and optimal TDDS. There are several methods mentioned for Drug and PSA (adhesive) interaction studies and some of the analytical methods used are FTIR spectroscopy and NMR spectroscopy methods.

i. Studies by FTIR spectroscopy.

FT-IR spectra were obtained with a Bruker Vertex 70 spectrometer using the KBr pellet coating procedure (Billerica, USA). Dropwise application of sample solution in ethyl acetate onto the KBr pellet followed by drying at 50 °C for 5 minutes. The spectra were obtained using 128 scans in the 4000–400 cm1 spectral region. OPUS software was used to process the spectral data (Bruker Optics, Billerica, USA). A functional group was part in an FT-IR investigation to investigate drug-PSA interactions. The ionic interaction between drug and functional groups of PSAs was evaluated using IR peaks in the bond to H area, double region, and fingerprint region. NMR data was used to further corroborate this.

ii. Studies by NMR spectroscopy.

Spectroscopy of solid-state NMR The solid-state NMR experiment was carried out on a 400 MHz Bruker Avance III-400 spectrometer (Billerica, USA) under 10 kHz magic angle spinning (MAS) conditions. To determine the chemical shift, an external standard of adamantine congressane was utilised.

13C solid-state NMR was used to confirm the ionic connection between PRO and AACOOH. ZAL's binding energies with AAnone, AAOH, and AACOOH were 4.06, 3.84, and 3.56 kcal/mol, respectively, indicating that ZAL was capable of forming comparatively stable complexes with three PSAs.

5.2 Adhesive molecular mobility studies

i. Studies by Thermal analysis

The PSA molecular stiffness and free volume forming ability were described using the glass transition temperature (Tg), which was employed as a measure of molecular mobility.[R-43.] The presence of a high Tg value usually suggests that PSA's molecular flexibility is weak and that the chances of generating free volume are slim. When compared to pure PSAs, the Tg values of PRO-AACOOH and ZAL-AAOH increased by roughly 6 and 3 degrees Celsius, respectively. The results showed that the molecular mobility of PSA in two formulae had dramatically decreased.

ii. Rheology study

The rheology investigation determined viscoelastic characteristics such as storage modulus (G'), loss modulus (G''), and phase shift angle (δ). The findings were used to confirm the PSA's stiffness and to depict the drug-PSA interaction from the perspective of PSA. To distinguish between PSA's solid-like and liquid-like qualities, the value of G''/G' was used to calculate the phase shift angle. A higher phase shift angle δ meant higher mobility of the PSA molecule. The results of strain sweep were showed (ω = 6.28 rad/s), viscoelastic modulus G′ and G ″ of PRO-AAnone, ZAL-AAnone, PRO-AAOH and ZAL-AAOH slightly decreased compared with their corresponding pure PSAs. G′ and G″ of PRO-AACOOH and ZAL-AACOOH increased significantly compared AACOOH.

VI. Conclusions

One of the most promising medicine delivery modalities is transdermal drug delivery. When compared to traditional dosage forms, it has various advantages, including continuous drug release, avoidance of the first pass effect, patient compliance, ease of application and removal in the event of toxicity, and a reduction in side effects. The challenge of developing and evaluating methods for high-quality transdermal patch development could be met by gaining a better understanding of available transdermal designs, polymer component selection and design (adhesives, backing membranes, penetration enhancers, plasticizers, etc.), transdermal system advantages, and typical evaluation parameters, as well as in vitro and in vivo studies. Greater understanding of the diverse mechanisms of biological interactions, as well as polymer, is essential to optimise this drug delivery method. As the next generation of drug delivery systems, TDDS has a realistic practical use.

Conflict of Interest

The authors reported no potential conflict of interest.

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Rajendra Herur Vishnumurthy. "Components and systematic evaluation of Transdermal drug delivery system: A review." *IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)*, 17(1), (2022): pp. 43-58.