TRANSDERMAL DRUG DELIVERY PATCHES: A REVIEW

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ABSTRACT

Despite making a substantial contribution to medical practice, transdermal drug delivery has not yet reached its full potential as a substitute for oral drug administration and hypodermic injections. First-generation transdermal delivery methods have slowly becoming more often used in clinical settings to administer small, lipophilic, low-dose medications. Clinical solutions have also been created using second-generation delivery methods such chemical enhancers, non-cavitational ultrasound, and iontophoresis; this latter method adds functionality by allowing for real-time adjustment of distribution rates. Targeting the barrier layer of the stratum corneum involves the use of microneedles, thermal ablation, microdermabrasion, electroporation, and cavitational ultrasound. In order to administer a specific dosage of medication into the body, a transdermal patch is an adhesive patch that is medicated.

KEYWORDS: proliposomes, transdermal patches, transepidermal absorption, transdermal drug delivery system, TRX, EVAC, and IPM.

Introduction: Oral and parenteral administration are the two most used drug delivery techniques, with oral administration accounting for the majority of small molecule drugs. The oral route offers the patient self-administration, mobility, and predetermined doses as advantages. These factors make ingesting drugs the most feasible method of administration. Both oral drug delivery and hypodermic injection can be effectively replaced by transdermal medication administration. Many topical formulations have been created in the present to treat local medical issues, and people have been applying chemicals to their skin for therapeutic purposes for thousands of years. The first transdermal drug delivery system for systemic use was authorized in the US in 1979.

DEFINITION

Transdermal drug delivery systems (TDDSs) are self-contained discrete dosage forms that, when applied to undamaged skin, distribute the drug(s) into the systemic circulation over an extended period of time at a predefined and predictable rate through the skin portal[1].

The goal of transdermal product dose design is to minimize drug retention and metabolism in the skin while increasing medicine flux through the skin and into the systemic circulation. Compared to injectables and oral approaches, transdermal administration is preferable because it increases patient compliance and prevents first-pass metabolism

First generation transdermal delivery systems

The bulk of transdermal patches currently being used in clinical settings originate from the first generation of transdermal delivery devices. Due to considerable improvements in patch technology and widespread adoption, the number of first-generation transdermal patches currently available on the market is on the rise (Box 2). The surge will eventually disappear, though, as drugs with suitable properties for such systems become harder to find. Candidates for first-generation delivery must be efficacious at low dosages, have a low molecular weight, and be lipophilic. Transdermal distribution should be more desirable than oral delivery due to insufficient oral bioavailability, the need or desire for less frequent dosage or consistent delivery patterns, or other factors[2].

Second generation transdermal delivery systems

The second generation of transdermal administration systems states that skin permeability enhancement is necessary to increase the range of drugs that can be applied topically. The ideal enhancer should avoid hurting deeper, living tissues and instead boost skin permeability by reversibly altering stratum corneum structure. It should also provide more driving force for transit into the skin. However, this generation's enhancement technologies—including non-cavitational ultrasound, iontophoresis, and conventional chemical enhancers—have had difficulty finding a balance between expanding distribution over the stratum corneum and preventing damage to deeper tissues. Due to the increased small-molecule dispersion for localized, dermatological, cosmetic, and certain systemic uses, this second generation of delivery technologies has predominantly advanced clinical practice. However, it has had little clinically relevant impact on the delivery of macromolecules[2].

Third-generation transdermal delivery systems:

The third generation of transdermal delivery systems is anticipated to have a substantial impact on medicine administration since it targets its effects to the stratum corneum. This targeting allows for a stronger disruption of the stratum corneum barrier and, as a result, more effective transdermal dispersion while preserving deeper tissues. In human clinical studies, it has been shown that novel chemical enhancers, electroporation, cavitational ultrasound, and more recently, microneedles, thermal ablation, and microdermabrasion31, can all transfer macromolecules over the skin in this manner. The creation of strategies to localize effects to the stratum corneum and the realization that the safety offered by localization should render more aggressive treatments medically acceptable both contributed to the development of these breakthroughs[2].

MECHANISM OF ACTION OF TDDS:

After application, the TDDS products' medicinally active ingredients penetrate the skin. They proceed to pass through the stratum corneum, the epidermis, the dermis, and peripheral capillary capillaries before dispersing throughout the body.

SKIN STRUCTURE
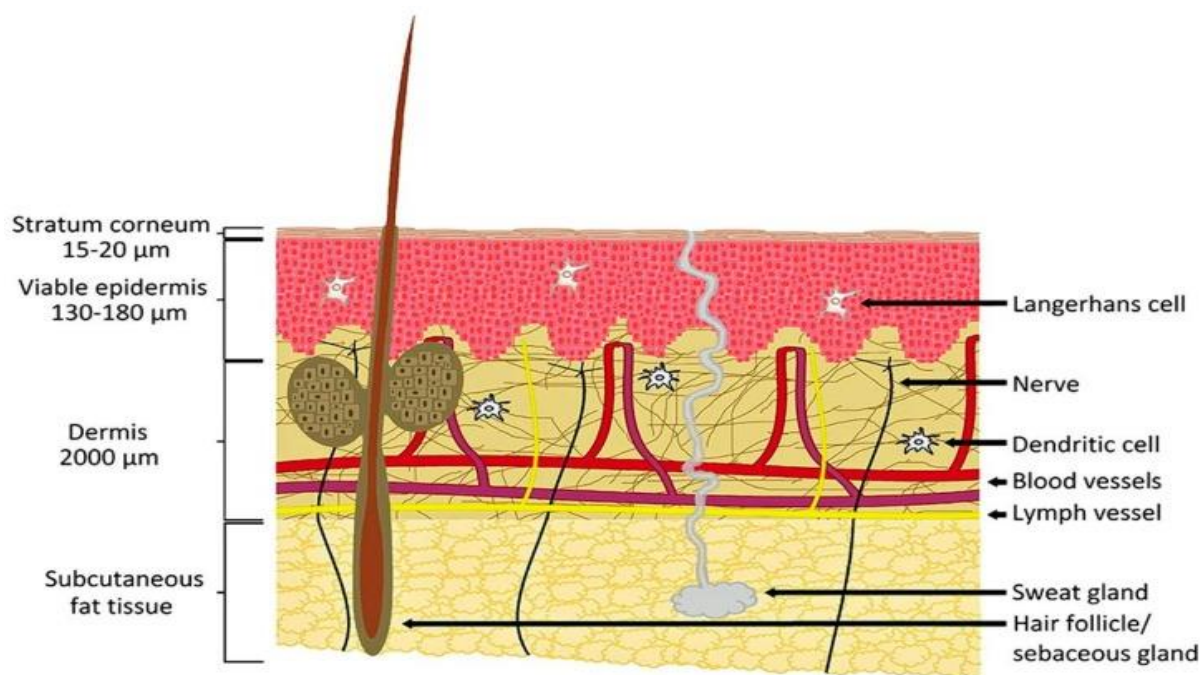
The largest and most visible organ of the body, the skin has a surface area of 1.7 m2, and makes up 16 percent of the average person's body mass. By serving as a barrier between the body and the outside world, the skin's principal function is to protect the body from pathogens, ultraviolet (UV) radiation, pollutants, allergies, and water loss. The three layers of skin are the epidermis, which houses the stratum corneum, dermis, which serves as an intermediary layer, and hypodermis, which is the innermost layer.

Epidermis

The epidermis, which is the skin's top layer, is around 0.8 mm thick on the soles of the feet and the palms of the hands. The viable epidermis is frequently referred to as the epidermal layers, and they are the multilayered regions of epithelial cells that make up the epidermal layers underneath the stratum corneum. The majority of cells in the epidermis, or keratinocytes, are found in the epidermal layers, which also contain melanocytes, Langerhans cells, and Merkel cells. The epidermis' stratum corneum is its outermost layer. It has direct contact with the outside environment, and its high density (1.4 g/cm3 in the dry state) and low hydration (15–20%) may contribute to its barrier qualities.

Dermis

The dermis, which gives the skin strength and suppleness, is about 2-3 mm thick and composed primarily of collagenous (70%) and elastin fibers. The dermis and epidermis are both nourished by dermal blood vessels. Besides neurons and macrophages, the dermis layer also has lymphatic veins.

Hypodermis

The skin's lowest layer, the hypodermis, commonly referred to as the subcutaneous layer, is composed of a network of fat cells. It is the layer that joins the body's deeper tissues, such muscles and bone, to the skin. Therefore, the primary functions of the hypodermis are physical shock absorption, heat insulation, and support and conductivity of the vascular and neurological impulses of the skin. About half of the body's fat is made up of fat cells that live in the hypodermis, with the remaining cells in the hypodermis being made up of fibroblasts and macrophages.

Drug Infiltration Pathways

There are two possible entrances for medication over healthy skin: transepidermal and transappendegeal channels. The stratum corneum, a multi-layered, multi-cellular barrier with a complex architectural pattern, is the first step in the transepidermal pathway that involves molecules flowing past it. transepidermal penetration that occurs intracellularly or between cells. Corneocytes, terminally matured keratinocytes, are capable of transporting hydrophilic or polar solutes intracellularly. Transport over intercellular gaps enables lipophilic or non-polar solute diffusion via the continuous lipid matrix. The transappendegeal route is used to transport molecules through sweat glands and hair follicles.

In order to design successful TDD systems, it is necessary to comprehend the kinetics of skin permeation. In assessing any TDD, examining chemical percutaneous absorption is a crucial step. Percutaneous absorption is the term used to describe how substances can permeate into different layers of skin and then cross the skin to enter the bloodstream. A step-by-step process called percutaneous absorption of molecules involves:

  i.   Penetration: The entry of a substance into a particular layer of the skin;

  ii.   Partitioning from the stratum corneum into the aqueous viable epidermis;

  iii. Diffusion through the viable epidermis and into the upper dermis;

  iv.   Permeation: The penetration of molecules from one layer into another, which is different both functionally and structurally from the first layer;

  v.   Absorption: The uptake of a substance into the systemic circulation[3].

TRANSDERMAL PATCHES

A transdermal patch, sometimes referred to as a skin patch, is an adhesive patch that is put to the skin to deliver a specific dose of medication into the bloodstream.

THEORY OF ACTION:

Percutaneous absorption is the term for the passive diffusion of chemicals via the skin. A permeation technique called transepidermal absorption involves penetrating the skin directly.

For transepidermal penetration, stratum corneum partitioning is necessary. After that, diffusion is applied to the tissue. The majority of substances are transported through the stratum corneum by the intercellular lipoidal pathway. The wet cell mass of the epidermis is where a penetrating medication enters when it penetrates the stratum corneum; however, because the epidermis lacks a direct blood supply, the drug must diffuse over it in order to reach the vasculature below. The viable epidermis is viewed as a single diffusion field in models. The majority of penetrants consider the permeable field to be a viscous watery regime. The epidermal cell membranes are tightly packed, and there is little to no intercellular space for ions and polar non-electrolyte molecules to diffuse through. Consequently, permeation necessitates numerous cell crossings.

TRANSDERMAL PATCH TYPES:

Drug-in-Adhesive with a single layer:

The sticky layer of this kind of patch contains the medicine in this type of patch. The adhesive layer is in charge of both releasing the medication and securing the system's several layers and overall structure to the skin. The adhesive layer is surrounded by a backing and a temporary liner.

RESERVOIR

The drug reservoir is kept in this system between the backing layer and the rate-controlling membrane. Additionally, a microporous rate membrane regulates medication release. The medicine may be present in the reservoir compartment as a solution, suspension, gel, or dispersed in a solid polymer matrix.

MATRIX

This system is a matrix of the two types.

a) Drug-in-Adhesive System: The medication is disseminated in an adhesive polymer, and the medicated polymer adhesive is then cast in a solvent or, in the case of hot-melt adhesives, melted and applied to an impermeable backing layer.

b) Matrix-Dispersion method: In this method, the drug is uniformly distributed within a hydrophilic or lipophilic polymer matrix. Furthermore, the drug-containing polymer is adhered to an occlusive base plate in a compartment constituted of a backing layer that is impervious to drugs. This method spreads adhesive throughout the circle rather than applying it to the face of the drug reservoir to create an adhesive rim.

Micro-Reservoir:

This system integrates matrix dispersion and reservoir technology. To create thousands of unleachable, microscopic drug reservoirs, the drug is suspended in an aqueous solution of a water-soluble polymer. This polymer is then uniformly disseminated in a lipophilic polymer.

Vapour patch:

In addition to holding the different layers together, a vapour patch's adhesive layer also emits vapour. Vapour patches, which release essential oils for up to 6 hours, are generally used for decongestion. Other on-the-market vapour patches improve sleep quality or aid smokers in quitting.

METHODS OF PREPARATION OF TRANSDERMAL PATCHES:

a) Asymmetric TPX membrane method.

b) Circular Teflon mould method.

c) Mercury substrate method.

d) By using "IPM membranes" method.

e) By using "EVAC membranes" method.

f) Preparation of TDDS by using Proliposomes.

g) By using free film method

A)Asymmetric TPX membrane method

Berner and John discovered the asymmetric TPX membrane method in 1994. A prototype patch can be created using heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter as the backing membrane. An adhesive is used to seal an asymmetric TPX [poly (4-methyl-1-pentene)] membrane over a concave membrane after the drug has been dispersed on it.

They are made using the dry or wet inversion technique. TPX is dissolved in a mixture of solvent (cyclohexane) and non-solvent additives at 60 °C to create a polymer solution. After being kept at 40°C for 24 hours, the polymer solution is cast onto a glass plate. After 30 seconds of 50°C evaporation of the casting film, the glass plate is immediately submerged.

B) Circular Teflon mould method.

Baker and Heller made the initial discovery of the circular Teflon mould method in 1989. A polymeric solution is used in various amounts as an organic solvent. The answer is then divided into two halves. In one section, the drug is dissolved, in the other, varying concentrations of enhancers are dissolved, and the two parts are then combined. The drug polymer solution is then given the plasticizer (such as Di-Nbutylphthalate). Prior to pouring the entire liquid into a Teflon mold, the mixture must be stirred continuously for 12 hours. Molds should be placed on a level surface and covered with an inverted funnel in a laminar flow hood model with an air speed of 0.5 m/s to control solvent vaporization. The solvent is allowed to evaporate for 24 hours. A dry film was then produced and preserved in a silica-filled desiccator after that.

C)Mercury Substrate Method :

In this technique, the medicine and plasticizer are dissolved in a polymeric solution. To prevent the solvent from evaporating, an inverted funnel is placed on top after it has been stirred for 10 to 15 minutes to create a homogenous dispersion.

D)Utilizing the "IPM Membranes" Method

The drug is dispensed and stirred for 12 hours in a magnetic stirrer in a solution of water and a polymer (propylene glycol containing Carbomer 940 polymer). Triethanolamine will make the dispersion more viscous and neutralized. Buffer pH 7.4 is used to produce a solution gel if the medicine has low solubility in aqueous solution. The developed gel will be incorporated into the IPM membrane.

By Using "EVAC Membranes" Method:

The production of TDS necessitates the use of a 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC), and rate control membrane. Propylene glycol should be used to make the gel if the drug is insoluble in water. Propylene glycol will be used to dissolve the medication, followed by the addition of Carbopol resin and neutralization with a 5% w/w sodium hydroxide solution. The medication is put on a backing layer sheet that covers the target area and is in the form of a gel. A rate-controlling membrane will be positioned over the gel, and the edges will be sealed with heat to create a leak-proof device.

Preparation of TDDS by Using Proliposomes:

Utilizing the carrier strategy and the film deposition process, proliposomes are created. The ideal ratio of the medication to the lecithin, according to earlier studies, is 0.1:2.0. Put 5 mg of mannitol powder in a 100 ml round bottom flask, keep it at 60 to 70 degrees, rotate it at 80 to 90 revolutions per minute, then vacuum dry it for 30 minutes to create proliosomes. After drying, the water bath's temperature is adjusted to 20–30°C. After thoroughly drying, a 0.5ml aliquot of the organic solution is added to the round-bottomed flask at 37°C. The medication and lecithin are dissolved in a suitable organic solvent mixture. After thoroughly drying, a 0.5ml aliquot of the organic solution is added to the round-bottomed flask at 37°C. The medication and lecithin are dissolved in a suitable organic solvent mixture. The flask containing the proliposomes is connected to a lyophilizer after the last loading step, and the drug-loaded mannitol powders (proliposomes) are desiccated overnight before being sieved through 100 mesh. A glass bottle is used to collect the powder and store it frozen until characterization.

By using Free Film Method:

First, a film devoid of cellulose acetate is made by casting it onto a mercury surface. To create a 2 percent weight-to-weight polymer solution, use chloroform. Plasticizers should be used at a concentration of 40% by weight of the polymer. Then 5 mL of the polymer solution is placed in a glass ring and set over the mercury surface in a glass petridish. The petridish can be used to control the pace of solvent evaporation by putting an inverted funnel over it. Check the mercury surface for layer formation once the solvent has entirely evaporated. The dry film will be divided and kept until needed in a desiccator between wax paper sheets. By changing the volume of the polymer solution, we may use this technique to create free films of different thicknesses[6].

COMPONENTS OF TRANSDERMAL PATCHES:[6]

a) Polymer matrix/ Drug reservoir

b) Drug

c) Permeation enhancers.

d) Pressure sensitive adhesive (PSA).

e) Backing laminate.

f) Release liner.

g) Other excipients like plasticizers and solvents

a. Polymer Matrix/ Drug Reservoir:

The drug is mixed with a synthetic polymer base that is either liquid or solid to create the formulation. With the medication and other system components like penetration enhancers, it should be chemically and biologically compatible. A medicine should be distributed by them reliably and efficiently for the duration of the product's claimed shelf life, and they should be secure. Transdermal drug delivery methods employ polymers categorized as

a) **Natural Polymers**: e.g., cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.

b) **Synthetic Elastomers**: e.g. polybutadiene, hydrin rubber, silicon rubber, polyisobutylene, acrylonitrile, neoprene, butyl rubber etc.

c) **Synthetic Polymers**: e.g. polyvinylalcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc

b)Drugs:

Some of ideal properties of drugs to be consider during preparation of Transdermal patches are as follows:

Sr no.	Parameters	Properties
1	Dose	Should be Low in weight (less than 20mg/day).
2	Half-life	10/less (hrs).
3	Molecular weight	<400da.
4	Skin permeability coefficient	0.5*10-3cm/h
5	Skin reaction	Non irritating, Non sensitizing
6	Oral bioavailability	Low

Table No. 1: Ideal properties of drugs [6]

c) Permeation Enhancers:

Chemicals that raise the stratum corneum's permeability in order to reach therapeutic drug candidate levels. To improve permeability, they engage in interactions with the stratum corneum.

a) Ideal Properties of Permeation Enhancers:

i. They should not irritate, poison, or cause allergies.

ii. They must not bind to the receptor site, implying that they have no pharmacological effect.

iii. They should have a pleasing appearance and feel on the skin.

d) Pressure Sensitive Adhesive (PSA):

It helps the transdermal patch adhere to the surface of the skin. It may be easily removed off a flat surface without leaving any residue. PSA examples include silicon-based adhesives, polyacrylates, and polyisobutylene**.**

d) Backing Laminate

It is a supportive ingredient resistant to drugs and permeation-increasing agents. It is crucial that the medication, enhancer, adhesive, and other excipients are chemically compatible.

Vinyl, polyethylene, and polyester films, for instance

f) Release Liner:

The most crucial packaging component for protecting the patch during application is this. It comprises of a base layer made of either an occlusive material (like polyethylene or polyvinyl chloride) or one that is non-occlusive (like paper cloth). It is created using Teflon or silicone. The release lining should allow the drug, penetration enhancers, and water to all pass through.

g) Other Excipients Like Plasticizers and Solvents:

a) Solvents: Chloroform, methanol, acetone, isopropanol and dichloromethane.
b) Plasticizers: Dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol[7]

EVALUATION PARAMETERS: [6]

a. Physicochemical evaluation
b. In vitro evaluation
c. In vivo evaluation

1. Physicochemical Evaluation:

(a) **Physical appearance**: Colour, clarity, flexibility, and smoothness of all created patches were visually evaluated.

(b) **Thickness**: At various spots on the transdermal film, the thickness is measured using a travelling microscope, dial gauge, screw gauge, or micrometre.

(c) **Uniformity of weight:** To explore weight variance, 10 randomly chosen patches were each weighed individually, then the average weight was calculated. Weights should not deviate much from the average. Drug content determination: Following the accurate dissolution of a precisely weighed quantity of film (about 100 mg) in 100 mL of a suitable solvent in which the drug is soluble, the solution is shaken continuously for 24 hours in a shaker incubator. After then, the entire solution is sonicated. After sonication and subsequent filtering, the drug concentration in the solution is measured spectrophotometrically**.**

(d) **Content uniformity test**: The contents of each of the ten patches are picked. If nine out of ten transdermal patches have content between 85 and 115 percent of the specified value and one patch has content between 75 and 125 percent of the specified value, the transdermal patches pass the content

uniformity test. Twenty more patches are examined for drug content if the composition of three patches is between 75% and 125%. The transdermal patches are considered to be effective if the results of these 20 patches fall between 85 and 115 percent.

(e) **Moisture content:** The made films are weighed separately and kept in a desiccator with calcium chloride for 24 hours at room temperature. The films are weighed again at a predetermined time interval until they display a constant weight. The % moisture content is calculated using the formula below. % Moisture content = Initial weight - Final weight multiplied by 100

(f) **Moisture Uptake**: In a desiccator, weighed films are kept at room temperature for 24 hours. These are then taken out and placed in a desiccator with a saturated potassium chloride solution at 84 percent relative humidity until a constant weight is achieved. Following is how the percentage moisture uptake is calculated:

   % moisture uptake is calculated as Final Weight - Initial Weight X 100.

(g) **Flatness: %** The surface of a transdermal patch should be smooth and shouldn't contract with time. The studies on flatness can support this. In order to determine how flat a patch is, three strips are cut—one from the center and two from each side. The length of each strip is measured, and the percent constriction method is used to determine the variance in length. Flatness at 100% is equivalent to constriction at 0%.

I1 - I2 X 100 = percent restriction I2 = Each strip's overall length I1 = The first strip's length Folding Endurance: The purpose of folding endurance testing is to ascertain the folding ability of films subjected to repeated, extreme folding situations. Folding endurance is determined by repeatedly folding the film in the same place until it breaks. The number of times a film can be folded in the same location without rupturing is known as its folding endurance value.

(h) **Tensile Strength**: To measure tensile strength, polymeric sheets are sandwiched between corked linear iron plates. One end of the films is secured by an iron screen, and the other is connected to a thread that can move freely thanks to a pulley. The pan is secured using the thread's hanging end as the weights are gradually put to it. A pointer on the thread is used to gauge the length of the film. It is claimed that the weight is just sufficient to cause the movie to break. Tensile strength can be calculated using the equation below. Tensile strength F/a b (1+L/l) F stands for the breaking force, and represents the film's breadth, b represents its thickness, L represents the film's length, and l represents the film's elongation at break. A polymer's tack characteristics are what allow it to adhere to a surface with little or no contact pressure. The molecular weight and composition of the polymer, as well as the use of tackifying resins in the polymer, all affect tack.

(i) **The thumb tack test:** The amount of force needed to pry the thumb away from the adhesive is a gauge of tack.

(j) **Rolling ball test**: In this test, the length of time a stainless-steel ball travels along an upward-facing adhesive is determined. If the adhesive is less sticky, the ball will move farther.

(k) **Quick stick (Peel tack) test** The peel force necessary to release the bond between the adhesive and the substrate is calculated by pulling the tape 90 degrees away from the substrate at a speed of 12 inches per minute. Tack is the amount of force required to continuously draw a probe away from an adhesive.

(l) **Folding endurance:** This test was performed to determine the strength of the patch created from various polymers and the effectiveness of the plasticizer. Folding endurance is the number of folds required to destroy any polymeric patch. The test for manual folding endurance involved repeatedly folding a 2 x 2 cm sheet of film until it broke. The number of times the patch could be folded in the same spot without breaking or cracking was used to calculate the value of folding endurance. Three of each type of patch were used in the test.

2.In vitro release studies:

(a)The Paddle over Disc: The transdermal system is connected to a disc or cell at the bottom of the vessel that retains medium at 32.5°C, much like the USP paddle dissolving device (PhEur 2.9.4.1/USP apparatus 5).

(b)The Cylinder modified USP Basket: (USP apparatus 6 / PhEur 2.9.4.3) Similar to the USP basket type dissolution apparatus, the system is attached to the top of a hollow cylinder that is submerged in medium at 32.5°C.

c) The reciprocating disc (USP apparatus 7) oscillates patches linked to holders in small amounts of media in this way, making the apparatus suitable for systems delivering low drug concentrations. Another choice is the paddle over extraction cell strategy (PhEur 2.9.4.2).

3.In vivo Studies:

(a) The most accurate way to determine a drug's efficacy is through in vivo studies. Variables that cannot be fully investigated in in vitro studies can be fully investigated in vivo. To assess TDDS in vivo, both human volunteers and animal models can be used.

(b)Animal models Small-scale animal experiments are used since human research takes a lot of time and resources. The most common animal species used to evaluate transdermal drug delivery systems are the mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, and guinea pig. According to the results of several investigations, hairless animals are preferred over hairy animals in both in vitro and in vivo testing. One of the most reliable in vivo models for analyzing the transdermal drug distribution in people is the Rhesus monkey.

(c)Human models The last phase of transdermal device development comprises gathering pharmacokinetic and pharmacodynamic data once the patch has been implanted in human participants. Clinical studies have been conducted, among other things, to assess efficacy, risk, side effects, and patient compliance. Phase II

clinical trials are used to determine short-term safety and efficacy in patients, while phase I clinical studies are used to assess same factors in volunteers. While phase IV post-marketing monitoring trials are intended to find adverse drug reactions in sold patches, phase III trials show safety and effectiveness in a significant number of patients. Although they are expensive and time-consuming, human trials are the best approach to gauge a drug's efficacy.

4.Skin irritation studies:

The research were conducted in accordance with the approved process after receiving ethical approval from the Panjab University, Chandigarh's Institutional Animal Ethical Committee (IAEC). The albino Wistar rats were housed in cages with free access to water and a lab meal. To prevent peripheral harm, the dorsal abdominal skin of the rats was painstakingly shaved prior to the testing. A transdermal patch was applied to the naked skin and covered with a non-sensitizing microporous tape. . A 0.8 percent v/v aqueous solution of formalin was employed as a common skin irritant. Every day for up to seven days, a fresh patch was given to the animals. The formulation was stopped after 7 days, and the erythema score was noted and compared to the norm. The erythema score, which ranged from 0 for no erythema to 1 for very weak erythema (light pink), 2 for well-defined erythema (dark pink), 3 for moderate to severe erythema (light red), and 4 for severe erythema (Draize et al. 1944), was read and recorded.

ADVANTAGES:

- ✓ Transdermal administration has clear advantages. Even the administration of therapeutic drugs is painless; the patient does not have to administer the injections themselves; there are no awkward delivery systems or potentially dangerous needles to handle; and the drug itself has few or no gastrointestinal side effects. Lower peak plasma levels of the medication lead to fewer side effects. Additionally, transdermal delivery is beneficial for drugs with a significant first-pass effect through the liver, poor oral absorption, frequent dosage, or reactions with stomach acid. A sizable portion of the drug is destroyed as a result of the first pass effect. On the other hand, drugs that are absorbed through the skin skip the liver and enter the bloodstream right away.
- ✓ Topical patches are a painless, non-invasive way to give the body chemicals.
- ✓ Topical patches are a more efficient way to give medications that are badly damaged by the liver, poorly absorbed from the gut, or broken down by stomach acids.
- ✓ Topical patches deliver medication over an extended length of time in a controlled, reliable manner.
- ✓ Compared to topical patches, oral medications and supplements have greater negative side effects.
- ✓ Topical patches are easier to remember to use and apply.
- ✓ Topical patches can be used as an alternative by those who are unable or unable to consume medications or dietary supplements orally.
- ✓ Topical patches have a modest price.

✓ The majority of people prefer topical patches[6].

LIMITATIONS:

For facile diffusion across the SC, a solute must have a molecular weight of less than 500 Da since solute diffusivity is inversely related to its size.

• For the permeant to successfully penetrate the SC and its underlying watery layers, a log P (octanol/water) of 1-3 is necessary for systemic distribution to take place.

• Human skin permeability varies both within and between individuals in both health and disease. This implies that biological responses will vary depending on the skin absorption profiles—fast, slow, and normal. Because intact SC is a barrier, it can only be utilized for very potent drugs that need very low blood concentrations to have a therapeutic effect (for example, nicotine requires 10–30 ng/ml).

• Pre-systemic metabolism; peptidases and esterases, which are found in the skin, may cause the drug to be metabolized into a therapeutically inactive form, reducing the medicine's effectiveness.

• Skin sensitivity and irritation, commonly referred to as the "Achilles heel" of dermal and transdermal administration. Erythema, oedema, and other symptoms in the skin can be brought on by exposure to particular stimuli, such as drugs, excipients, or parts of delivery systems. The skin acts as an immunological barrier[7].

FACTORS AFFECTING TRANSDERMAL PATCHES:

There are various factors which affects the action of transdermal patches. These are given below

a. Physicochemical Properties

a) Partition coefficient
b) Molecular size
c) Solubility/melting point
d) Ionization

b. Physiological & Pathological Conditions of Skin

a) Reservoir effect of horny layer
b) Lipid film
c) Skin hydration
d) Skin temperature
e) Regional variation
f) Pathological injuries to the skin
g) Cutaneous self-metabolism[8]

MARKETED PREPARATION:

Transdermal drugs approved by USFDA[2]

Drug/product name	Approved year	Indication
Scopolamine/Transderm-Scop	1979	Motion sickness
Nitro-glycerine/Transdermal-Nitro	1981	Angina pectoris
Clonidine/Catapres-TTS	1984	Hypertension
Estradiol/Estraderm	1986	Menopausal symptom
Fentanyl/Duragesic	1990	Chronic pain
Nicotine/Nicoderm, Habitrol, ProStep	1991	Smoking cessation
Testosterone/Testoderm	1993	Testosterone deficiency
Lidocaine with epinephrine (iontophoresis)/Iontocaine	1995	Local dermal analgesia
Estradiol with norethidrone/Combipatch	1998	Menopausal symptoms
Lidocaine/Lidoderm	1999	Post-herpetic neuralgia pain
Ethinyl estradiol with norelgestromin/Ortho Evra	2001	Contraception
Estradiol with levonorgestrel/Climara Pro	2003	Menopausal symptoms
Oxybutynin/Oxytrol	2003	Overactive bladder
Lidocaine (ultrasound)/SonoPrep	2004	Local dermal anesthesia
Lidocaine with tetracaine/Synera	2005	Local dermal analgesia
Fentanyl HCl (iontophoresis)/Ionsys	2006	Acute postoperative pain
Methylphenidate/Daytrana	2006	Attention deficit hyperactivity disorder
Selegiline/Emsam	2006	Major depressive disorder
Rotigotine/Neupro	2007	Parkinson's disease
Rivastigmine/Exelon	2007	Dementia

Table No. 2: Transdermal drugs approved by USFDA[2]

FUTURE OF TRANSDERMAL DRUG DELIVERY SYSTEM:

Future developments in drug delivery systems include liposomes, niosomes, and micro emulsion. This study aims to enhance the delivery of pharmaceuticals with low intrinsic solubility in the majority of conventional excipients. Among the potential drugs for administration are steroids, antifungal, antibacterial, interferon, methotrexate, and local anesthetics. With a recent annual growth rate of 25%, the transdermal patch market is anticipated to rise in the future. This number will increase as more transdermal medications are released and

as new devices become accessible. Transdermal analgesic delivery will undoubtedly become more common as design advances. Research is being done in an effort to increase safety and effectiveness. to provide more precise drug distribution with a longer duration of action, as well as to improve practical factors such as the patch wearer's experience. Another potential advancement is improved transdermal technology, which alters the skin barrier or amplifies the energy of the drug molecules to increase drug flux across the skin. Following the popularity of iontophoresis-based patches, researchers are now looking at other 'active' transdermal technology modalities.

These include thermal energy (uses heat to make the skin more permeable and to increase the energy of drug molecules), sonophoresis (uses low-frequency ultrasonic energy to disrupt the stratum corneum), and electroporation (uses high-voltage electrical pulses to form transitory aqueous pores in the skin). Studies have been done on magnetophoresis, or the application of magnetic energy to increase drug flux over the skin. The transdermal patch may be an underutilized therapeutic for the treatment of both acute and chronic pain.

We anticipate that this method of medication distribution will become more well-liked and practical with improved delivery and a wider selection of analgesics. With over 40% of drug delivery candidate items in clinical trials associated to the transdermal or dermal system, the transdermal route of drug delivery is now the most successful novel research topic in new drug delivery system. As an alternative, secure, and convenient method of administering systemic medications, transdermal drug delivery systems (TDDS) were developed.

Systemic drug administration via the skin has a number of benefits, such as keeping a constant drug level in blood plasma, fewer side effects, higher bioavailability by avoiding hepatic first-pass metabolism, and increased patient adherence to the treatment plan. As it provides for continuous medication release into the systemic circulation, skin has recently been recognized as the safest port for drug delivery[9].

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