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TRANSDERMAL DRUG DELIVERY SYSTEM

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Abstract

By applying a medication formulation to healthy, intact skin, a transdermal drug delivery device delivers pharmaceuticals systemically in a painless manner. Without building up any medication in the dermal layer, the medication first enters the body through the stratum corneum before moving on to the deeper dermis and epidermis. In order to avoid the nausea and vomiting that come with motion sickness, transdermal medication administration was initially employed in 1981. It promotes the healing of bodily injuries. Transdermal drug delivery involves applying a medicated adhesive patch to the skin in order to penetrate the epidermis and enter the bloodstream and administer a prescribed dosage of medication.

It facilitates the healing of an injured bodily component. Using a transdermal patch allows for a controlled release of medication into the patient, which is advantageous over other delivery methods like oral, topical, intravenous, i.m., etc. Typically, this is accomplished by either a porous membrane covering a reservoir of medication or by body heat melting thin layers of medication embedded in the adhesive. The primary drawback of transdermal administration systems is that, because the skin acts as a very strong barrier, only small-molecule drugs may easily pass through the skin and be administered this way. This review article provides an overview of transdermal patches, outlining their types and preparation techniques.

An effective transdermal medication delivery method was developed. The medication in TDDS readily permeates the skin and reaches the intended location. Transdermal drug delivery methods were created to circumvent the issues associated with oral medication delivery. Since 1981, these systems have been used as dependable and safe means of delivering medications.

1) Introduction:-

Any device that is membrane-moderated is considered transdermal. Although the oral route is the most widely used and well-liked method of prescription administration, it has several drawbacks, such as first pass metabolism and drug breakdown in the gastrointestinal tract because of enzymes, pH, and other variables. The goal shared by the pharmaceutical industry and all researchers is to develop a safe and effective medication delivery mechanism.

Transdermal delivery systems are used to apply medication topically in the form of patches that apply medication at a fixed, regulated pace for systemic effects. Safety, increasing the efficacy of pharmaceuticals, and patient compliance are the main goals of controlled drug delivery. A medication can be applied topically and progressively released into the bloodstream via a process called transdermal drug delivery.To enable the medication to permeate into the bloodstream, a transdermal patch is a medical device applied topically and remained on the skin for an extended period of time.

By putting a medication formulation to healthy skin, medicines can be systemically delivered by an alternate method known as transdermal drug delivery. TDDS is an essential part of an innovative drug delivery system. One of the newest and most effective ways to administer medications is through the transdermal route.

Transdermal patches, which come in various sizes and are flexible pharmaceutical compositions, contain one or more active ingredients. The drug enters the body through the stratum corneum, passes through to the deeper dermis, and then reaches the epidermis without building up any accumulation in the dermal layer.

This device provides an extra method of medicine delivery. Transdermal medicine administration is among the most effective and reliable techniques.

Transdermal drug delivery systems (TDDS) are devices that have specified surfaces, are filled with active compounds, and are intended to administer an amount of the active ingredient to the surface of intact skin at a programmed rate. (1)

1.1) History:-

Topical treatments that are designated, bandaged, rubbed, or applied to the skin are definitely been around since the beginning of human history. Written records of these techniques, such those found on Sumerian clay tablets, demonstrate how long ago that these methods were being utilized .

In fact, according to Henshilwood et al. (2011), there is evidence that a liquid mixture rich in ochre, which was created approximately 100,000 years ago and discovered at the Blombos Cave in South Africa, may have been employed as skin protection and ornamentation. For their cosmetic and dermatological preparations (unguents, creams, pomades, rouges, powders, and eye and nail paints), the ancient Egyptians employed oil (which included castor, olive, and sesame), fats (mostly animal), scents (such as bitter almond, peppermint, and rosemary), and additional components (Forbes, 1955

Compounding herbal medicines and other excipients into dosage forms was initially performed a millennium and a half later by the Greek physician Galen (AD 129–199). Galenic pharmacy is the name given to his methods, and he is recognized as the "Father of Pharmacy" by many. The most famous formula that Galen created is possibly Cerate (Cérat de Galien), a cold cream (Figure 1B) with a composition that is essentially the same as what is used today (Bender and Thom, 1966). Transdermal patches (emplastra transcutanea) are the

early equivalent of medicated plasters (emplastra), which were traditionally applied to the skin for local conditions and date back to Ancient China (c. 2000 BC).

A good deal of these early plasters were made up of various herbal medicine elements that were mixed with an adhesive natural gum rubber foundation and mounted to a paper or cloth backing support (Chien, 1987).

When Paracelsus existed from 1493 to 1541, a transdermal agent known as nicotine was already employed in a plaster called Emplastrum opodeldoch (Aiache, 1984).(1)

1.2) Composition of skin(2):-

The skin occupies an area of approximately twenty square feet, resulting in it being the biggest organ in the body. The organ in the body that is easiest to access is the skin. Its main purposes are sensation, temperature control, water output control, and protection. The average adult's skin has a surface area of 2 square meters, varies in thickness from around 1.5 to 4 mm, and weighs about 2 kg. Skin helps control body temperature, shields us from germs and the environment, and allows us to feel touch, heat, and cold.

Human skin consists of three well defined but mutually dependent tissues:

- The stratified, vascular, cellular epidermis
- Underlying dermis of connective tissues and
- Hypodermis.

Transdermal patches function gradually. The medication is put in a reasonably high dose to the inside of the patches, which are to be worn on the skin for a lengthy amount of time, and via the diffusion process, it directly enters the bloodstream through the skin. Because there is a high concentration on the patches and a low concentration in the circulation, the medicine will continue to diffuse into the blood from the patches for a longer amount of time through the diffusion process. This will help you maintain a steady medicine concentration in your bloodstream.

Following are the three pathways, through which the drug can penetrate through the skin:-

1. Through the Sebaceous Gland

2. Through the Sweat ducts

3. Through the hair follicles.

The first layer of skin is called the stratum corneum, or epidermis. It functions as a rate-limiting barrier to the penetration of different substances via the skin. The stratum corneum is very lipophilic and only holds 20% of its total water content. Depending on its level of hydration, it can have a thickness of 10–15 µm and a density of 1.4 g/cm3. Dried dead corneocytes and enhanced keratin fibers measuring 40 µm in width and 0.2–0.4 µm in thickness are seen in the stratum corneum.

The stratum corneum's lipids stop the body from losing too much water. The epidermis is a multilayered membrane with a thickness ranging from 75 to 150 µm. Its nature is hydrophilic. With a thickness of around 3-5 µm, the dermis is made up of

The stratum corneum's first layers reorganize to create wide intercellular lipid lamellae, which subsequently unite to form lipid bilayers. The behavior of the lipid phase differs from other biological membranes because of the lipid composition of the stratum corneum. Water is a crucial component of the stratum corneum because it produces natural moisturizing factor, which keeps the stratum corneum supple, and it also functions as a plasticizer to keep the stratum corneum from splitting. Finding the main drug penetration route through the stratum corneum is crucial to comprehending the physicochemical characteristics of the diffusing drug and vehicle effect throughout the stratum corneum. A chemical enters and diffuses through the keratinocyte via route 27 of the transcellular route, but first However, the molecule needs to split into and diffuse across the estimated 4–20 lipid lamellae between each keratinocyte in order to proceed to the next one. Most medications do not like this process of partitioning into and diffusing across several hydrophilic and hydrophobic domains. As a result, the intercellular pathway is currently thought to be the main mechanism that most medications pass through the stratum corneum.(2)

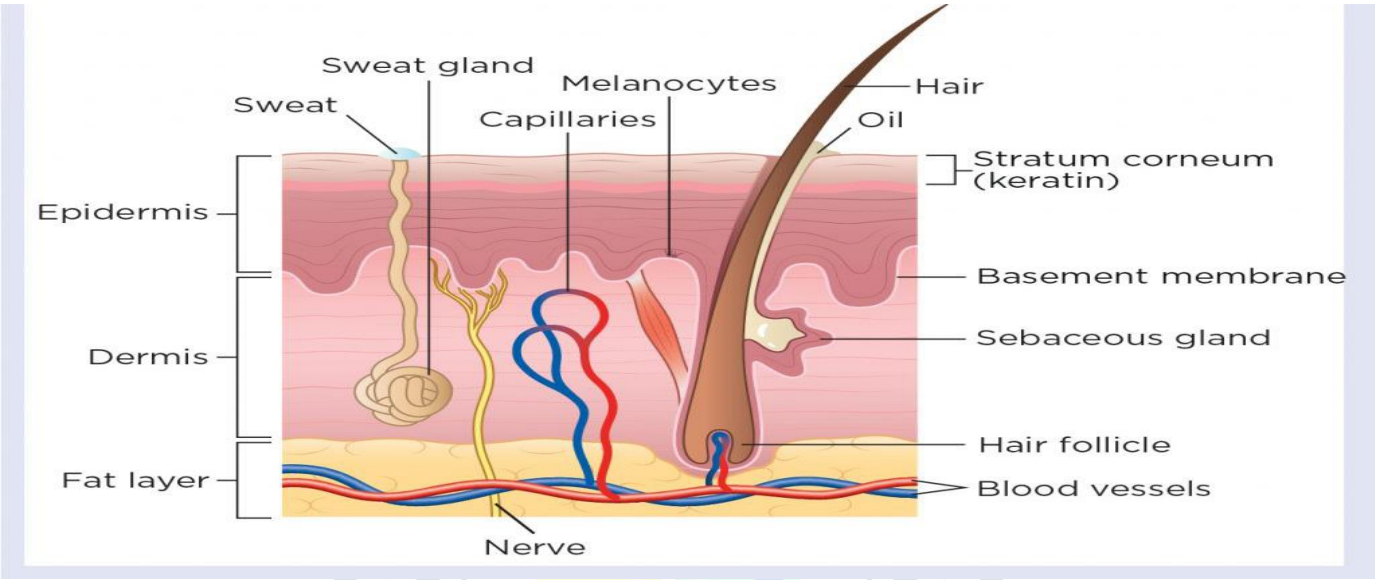


Fig no. 1 Composition of Human Skin

1.3) Types of Transdermal Patches (3):-

A. Matrix type
B. Reservoir type
C. Drug-in-adhesive
D. Multilaminate type

A)Matrix type transdermal patches:

This system is of two types

a) Drug-in-Adhesive System: The process of creating a drug reservoir involves dispersing the drug in an adhesive polymer and then applying the medicated polymer adhesive onto an impermeable backing layer either by solvent casting or, in the case of hot-melt adhesives, by melting the adhesive.

b) Matrix-Dispersion System: The medication is uniformly distributed in a hydrophilic or lipophilic polymer matrix in this approach. Additionally, this drug-containing polymer is attached to an occlusive base plate within a compartment made of a backing layer that is impermeable to drugs. Instead of placing the adhesive on the drug reservoir's face to create an adhesive rim strip, this approach spreads it around the circle.

B) Reservoir type transdermal patches:

This system maintains the drug reservoir sandwiched between a rate-controlling membrane and the backing layer. moreover, medication releases via a microporous membrane with rate control. The drug may be distributed throughout the reservoir compartment in a solid polymer matrix or as a solution, suspension, gel, or other form.

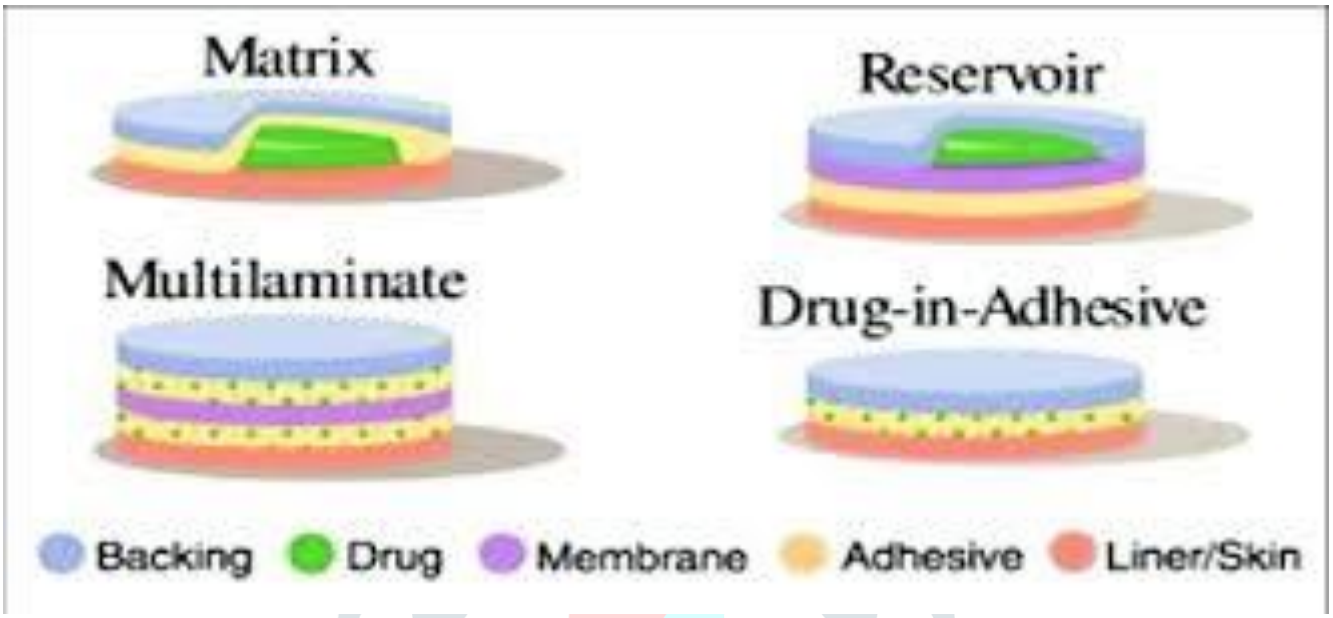


Fig No. 2 Types of Transdermal Patches

C) Single-layer Drug-in-Adhesive System:

This arrangement keeps the medication reservoir placed between the backing layer and a membrane that controls flow. Moreover, drug released through a rate-controlled microporous membrane. The medication may be dispersed in the reservoir compartment as a solution, suspension, gel, or another form, or it may be in a solid polymer matrix.

D) Micro-Reservoir System:

Reservoir and matrix-dispersion systems are combined in this system. wherein a drug is suspended in a water-soluble polymer aqueous solution, and the solution is then uniformly dispersed in a lipophilic polymer to produce thousands of microscopic, inaccessible drug reservoir spheres.

1.4) Elements Influencing the Transdermal Medication Delivery System (4)

Transdermal patches function differently based on several factors, including:

A) Elements of Physicochemistry

B) Anatomical Elements

C) Factors of Formulation

A) Elements of Physicochemistry

- Drug concentration,
- Molecular size and structure,
- Partition coefficient,
- Stability and half-life of the patch or drug inside the patch,
- Solubility/melting point,
- Ionization

B) Physiological Factors:

- Skin pH
- Skin hydration
- Application site
- Skin pathology
- Lipid films over the skin
- The reservoir effect of the horny layerLipid films
- Skin temperature
- Regional variation
- Pathological injuries to the skin
- Cutaneous self-metabolism
- Skin barrier properties in neonates and young infants
- Skin barrier properties in elderly skin;
- Penetration enhancers used

C) Formulation Factors

- Enhancers for Permeation
- Drug or Patch Release Characteristics
- Vehicle pH

D) Environmental Factors

- Oral Tissue Movement
- Saliva
- Salivary Glands

1.5) Advantages and Disadvantages (5):-

Table No. 2 Advantages & Disadvantages

Advantages	**Disadvantages**
a) Drug metabolisms that are first pass are avoided. b) Incompatibilities with the digestive system are avoided. c) It is possible to self-medicate. d) It has a significant benefit for individuals who are unconscious or nauseous. e) Since transdermal distribution avoids direct effects on the stomach and intestine, medications that disturb the digestive system may be suitable candidates for this mode of administration.	a) The possibility of allergic reactions, such as itching, rashes, local edema, etc., at the application site. b) Drugs with larger molecular sizes (over 1000) have more difficulty being absorbed. b) Could result in allergic responses. d) It is important that the molecular weight be less than 500 Da. e) Adequate lipid and aqueous solubility; permeate must have a log P (octanol/water) of 1 to 3 in order to cross the SC and penetrate underlying aqueous layers.

1.6) Application (6,7)

- Sometimes, patches instead of sublingual pills are used for the treatment of angina.
- Motion sickness is often treated with transdermal scopolamine.
- It is also possible to deliver vitamin B12 via a transdermal patch.
- One very stable type of vitamin B12 that works well with transdermal patches is cyanocobalamin
- Neurodegenerative disorders
- Cancer
- Infectious disease
- Gastrointestinal disease

3) Aims and objectives:

Aim:

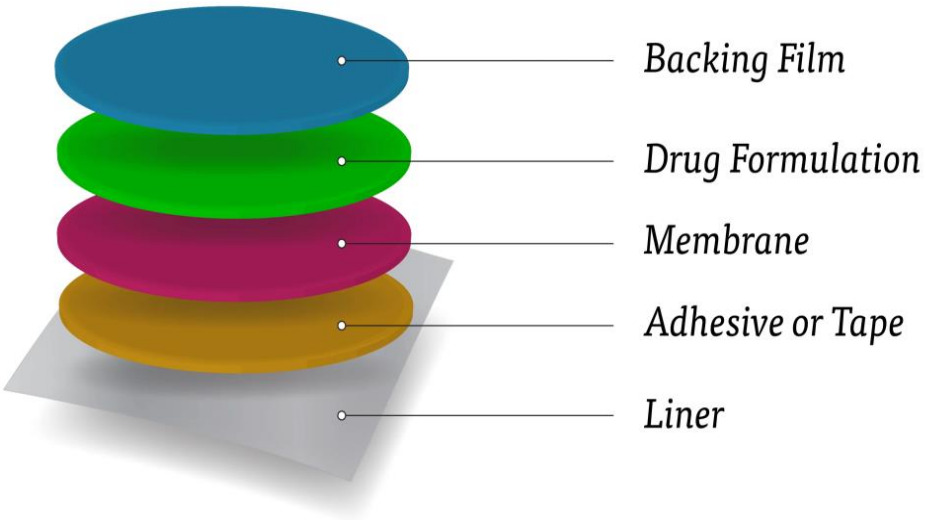
To study the transdermal drug delivery system because it is simple to use, reduces gastric irritation, stops hepatic first-pass metabolism, stops drug degradation in the stomach, releases medication continuously, and increases patient compliance.

Objective:

- To study the formulation of drug which is both safe and effective
- Transdermal delivery is used to administer drugs topically. In the form of patches that, for systemic effects, administer drugs at a fixed, controlled rate.
- Drugs that cause gastrointestinal upset can be good candidates for transdermal delivery because this method avoids direct effects on the stomach and intestine.

4) Components of the TDDS (8,9,10):-

The main components of the transdermal drug delivery system are as follows:-



- **Polymer matrix:-**

The medicine is manufactured by dispersing it in a synthetic polymer base, either in liquid or solid state, which regulates the drug's release from the device.

1. It should be chemically and biocompatible with the medication, among other perfect qualities.
2. The polymer ought to be non-toxic and stable.
3. The polymer shouldn't be very expensive.
4. The polymer and its breakdown product ought to be non-toxic or non-host hostile.

Types of polymers according to source:

Table no. 1 Types of Polymer

Natural polymers	Semi-synthetic polymers	Synthetic polymers
Ex- gelatin, natural rubber, Gums, waxes	Ex- acrylonitrile, Polybutadiene, neoprene	Ex- polyvinyl-alcohol Polyacrylate Polyamide, Polyethylene

- **Drug reservoir:**

Medication solution in close proximity to the release liner. Since selecting the medication ingredient is the most crucial decision in the effective implementation of a transdermal treatment, it should be done carefully

A medication should have the following ideal qualities:

- It weighs less than 600 Daltons molecularly.
- It ought to be harmless and non-irritating.
- It ought to have strong affinities for both lipophilic and hydrophilic phases.
- The medication's melting point need to be low

- **Backing layer:**

Chemical resistance and inertness to other components in the delivery system are essential qualities for the backing layer's substance. Some of the examples include 3M Scotchpak Backing 1006, silicone oil, EVA, and Polyisobutylene [21].Protecting the drug reservoir from the atmosphere and supporting the overall system are its functions .

- **Permeation enhancer *:-***

Chemical substances known as "permeation enhancers" effectively and reversibly reduce the stratum corneum barrier's protective qualities; enabling medications penetrate deeper skin layers and enter the bloodstream. Agents that can transfer the sorption of medications from drug delivery systems onto the skin are known as penetration enhancers or promoters. They are substances without any inherent medicinal qualities. It is theorized that penetration enhancers work on one or more of the layers to improve skin penetration.11 Drug flow across the skin can be expressed as follows: J = D Xdc/dx [24]. N. K., C.

Where, D- diffusion coefficient, C- concentration of the diffusing species,

x - Spatial coordinate

- **Solvent:**

Methanol, ethanol, dichloromethane, and acetone are among the solvents used in transdermal patch manufacture. The medication reservoir uses solvents.

These compounds increase penetration possibly by:

1). Swelling the polar pathways in the skin.

2). Fluidization of lipids.

- **Surfactants:**

The head group and the length of the hydrocarbon chain determine a surfactant's capacity to modify penetration. Anionic surfactants have a high skin-interaction potential and can permeate the skin. .

According to reports, the surfactants listed below improve penetration. Lauryl ether, Sorbian mono palmitate, sodium lauryl sulfate, sodium diactyl sulfo succinate, and so forth

- **Plasticizer**:

Ex- Dibutylpthalate, triethylcitrate,

Polyethylene glycol and propylene glycol.

- **Release Liner:**

Release liners keep drugs from migrating into the adhesive layer and from getting contaminated while they are being stored. Before a transdermal patch is put to the skin, a layer of protective material covering it is instantly removed. The primary package includes this layer. ex- BIO PSA HighTack 7-4301, BIO PSA MediumTack 7-4201, Scotch Pak 1022, Scotch Pak 1006

Other Excipients:

Excipients mainly contains following:

1.Adhesives:-

Transdermal devices have traditionally been attached to the skin using a pressure-sensitive adhesive. The device's front or back, with the pressure-sensitive adhesive extending peripherally, are the possible placements for the adhesive.

Ideal properties of adhesives:-

- Should be easily removed.
- Should not leave an unwashable residue on the skin.
- Should have excellent (intimate) contact with the skin
  At macroscopic and microscopic level.

2. Pressure sensitive Adhesives:

It facilitates a transdermal patch's increased adhesion to the skin's surface. It may be removed from the smooth surface with ease and without leaving any trace. .

a) Polyacrylates b) Polyisobutylene c) Silicon based adhesives

5) Evaluation parameters (11,12):-

1) Physical Appearance

Every transdermal patch is photographed to assess its smoothness, color, and flexibility.

2) Folding endurance

The film is folded till it breaks. Film's folding endurance is established by the point at which it can be folded without breaking. An area-specific strip is to be cut uniformly, and then folded in the same spot repeatedly until it breaks. The value of folding endurance decides by the number of times the film could be folded in the same way without breaking.

3) Film thickness

Using a digital micrometer, the thickness of the drug-loaded patch is measured at several sites, and the thickness of the newly developed patch is ensured by calculating the average thickness and standard deviation. Transdermal film thickness can be measured at various film sites using a micrometer, screw gauge, or traveling microscope dial gauge.

4) Shear Adhesion Test

The aim of this test is to determine an adhesive polymer's cohesive strength. The molecular weight, degree of cross-linking, polymer composition, kind, and quantity of tackifier used can all have an impact. A stainless steel plate is covered with adhesive-coated tape, and to cause the tape to pull in a direction parallel to the plate, a predetermined weight is suspended from it. The time it takes to remove the tape from the plate is used to calculate shear adhesion strength. Greater shear strength results from longer removal times.

5) Moisture content

The prepared patches are divided into precisely measured strips. Following individual weighing, the strips are stored for 12 hours at 300C in a desiccator that contains activated silica. Each film is reweighed one at a time until the weight remains consistent.

$$\% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight} \times 100}{\text{Initial weight}}$$

6) Weight uniformity

By weighing ten distinct, randomly chosen patches and computing the average weight and standard deviation, weight homogeneity may be ascertained. The average weight of each patch cannot be significantly different from any one patch's weight.

7) Thumb tack study

In this objective test, the thumb is momentarily pressed into the adhesive to be evaluated.

8) Quick test

Another name for it is the peel tack test. In this test, the tape is pulled at a speed of 12 inches per minute and 90ºC away from the substrate. Tack value, which is given in kilograms or grams per inch width, is a measurement and record of the peel force needed to break the binding between adhesive and substrate.

9) Skin irritation test

Testing for skin sensitivity and irritation can be done on healthy rabbits weighing between 1.2 and 1.5 kg on average. The rabbit's dorsal surface (50 cm2) needs to be cleansed. The hair should be shaved off of the clean region, and rectified spirit can be used to clean the surface before representative formulations are applied to the skin. After 24 hours, the patch is to be taken off, and the skin is to be examined, with the degree of the skin injury being divided into 5 grades.

10) Probe tack test

The measurement of tack is the amount of force needed to draw a probe away from the sticky polymer at a set rate. When determining the force necessary to break the binding of a pressure-sensitive adhesive surface in a transdermal patch, the thumb test can be substituted with the examining tack test . Plotting force vs. time shows how much force is needed to break the bond over a given period of time.

6) Marketed formulations(13):

Table no.3 marketed formulations

PRODUCT	TYPES OF TRANSDERMAL PATCHES	PURPOSE
Habitraol	Drug in Adhesive	Smoking cessation
Deponit	Drug in adhesive	Angina pectoris
vivelle	Reservoir	Postmenstrual syndrome
Captopress TTS	Membrane	Hypertension
nitrodisc	Microreservior	Angina pectoris
fematrix	Matrix	Postmentrual
NuPatch 100	Drug in adhesive	Anti-inflammatory
Esclim	Matrix	Parmone replacement therapy
Climara	Reservior	Postmenstrual syndrome
Lidoderm	Drug in adhesive	Anaesthetic

Fig No: 3 Transdermal Formulations

7) Future trends:

- Numerous medications, including steroids, methotrexate, interferon, antifungals, and antibiotics, are being developed for possible administration.
- As long as design advancements are made, transdermal analgesic administration is expected to gain more and more traction. To give more accurate medication distribution linked to longer duration of action, as well as to enhance practical aspects like the patch wearer's experience.
- Improved transdermal technology, which uses mechanical energy to boost drug flux through the skin by changing the skin barrier or raising the energy of the drug molecules, is another possible enhancement.
- Following the effective development of iontophoresis patches, different "active" transdermal technologies are being researched for a range of medications.
- These include sonophoresis, which uses low-frequency ultrasonic energy to disrupt the stratum corneum, thermal energy, which uses heat to increase the energy of drug molecules and make the skin more permeable, and electroporation, which uses short electrical pulses of high voltage to create temporary aqueous pores in the skin.
- This approach aims to increase the administration of medication that is inherently less soluble in the majority of traditional formulation excipients. Numerous possible delivery medications, including steroids, methotrexate, interferon, antifungal, and antibacterial agents, being developed.
- Systemic drug delivery via skin has a number of benefits, including maintaining a steady drug level in blood plasma, fewer adverse effects, enhancing bioavailability by avoiding hepatic first pass metabolism, and boosting patient adherence to treatment regimen.(49)

8) Conclusions:

The easiest approach to administer a certain dosage of medication to a certain location is by using a transdermal patch. They can use transdermal patches with relatively few negative aspects in addition to the benefits. A precise, preset medication is delivered by transdermal patches using transdermal drug delivery systems, which absorb the medication through our skin and into our circulation. Nowadays, a lot of new research is being conducted to use this method to combine newer medications. In order to maximize patient care, transdermal dosage forms may give physicians the chance to provide their patients more treatment options.

Enhancers with little toxicity can be designed with improved understanding of how enhancers interact with the stratum cornea and how structure-activity relationships are developed for enhancers. This article offers insightful insights about transdermal drug delivery systems and the evaluation procedure for them.

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