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Developing Transdermal Drug Delivery Systems: A Review

An alternative for Oral drug delivery

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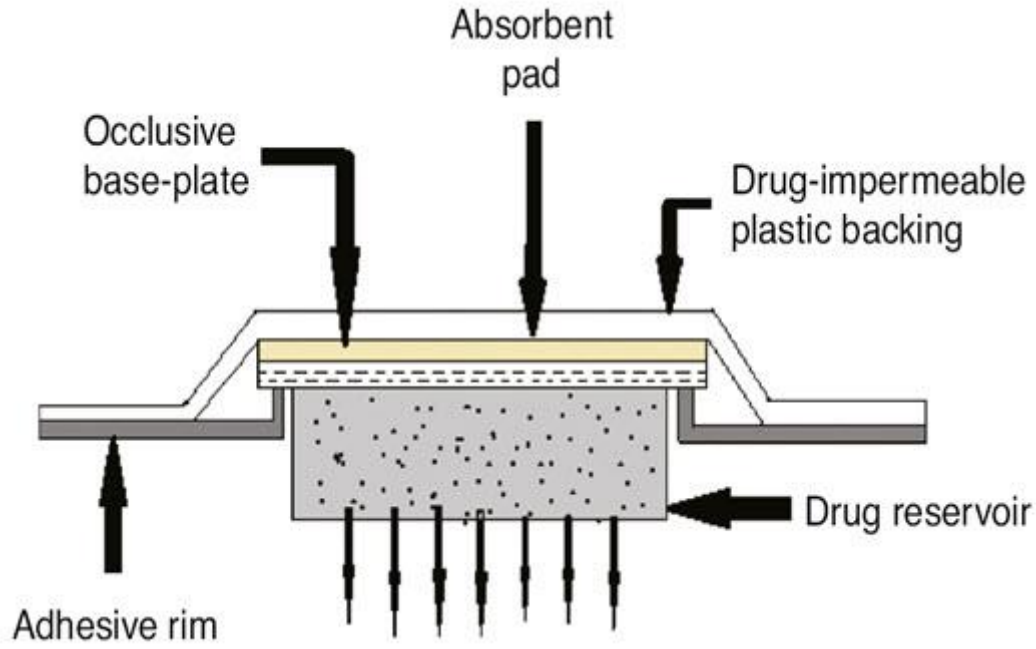
Abstract : This review article aims to provide a overview of Transdermal drug delivery systems (TDDS).also known as "patches," this are dosage forms that are designed to disperse a therapeutically effective amount of medication across a patient's skin in order to get systemic effects. this review paper encapsulates the multifaceted world of transdermal drug delivery systems, emphasizing their pivotal role in modern drug delivery, and their potential to reshape healthcare by providing effective, patient-centric, and therapeutically precise solutions. The insights gleaned from this review contribute to the ever-expanding knowledge base in the field and inspire future innovations in TDDS research and development. This review also spotlights recent clinical applications and therapeutic breakthroughs achieved through TDDS, ranging from pain management and hormone replacement to neurodegenerative disorders and pediatrics care. As we journey through these advances, it becomes evident that transdermal drug delivery is not only evolving but also revolutionizing the pharmaceutical care

Keywords :- Transdermal medication delivery system, patch, topical administration, and systemic circulation related terms.

I. INTRODUCTION

By putting a drug formulation to healthy skin, transdermal drug delivery is a painless means of administering medications to the body. The stratum corneum is first penetrated by the medication, which then moves into the deeper epidermis and dermis without accumulating in the dermal layer.
. The skin was first employed as an administration site for long-term drug delivery in the tenth century, and TDDS is an essential component of innovative drug delivery systems. One of the most trustworthy and efficient methods is transdermal medication delivery. One of the most effective and cutting-edge medicine delivery methods is transdermal (3). The first time this technology was used was more than 20 years ago. . In the 1980s and 1990s, the technology attracted a lot of attention from top pharmaceutical companies. By the middle to end of the 1990s, the trend of transdermal medication delivery system businesses joining forces with bigger businesses.
In this method, drugs for systemic effects are delivered topically using patches at a regulated and predetermined rate. The most widely used systems for dermatological problems in the past were topically administered lotions and ointments.
Creating a novel delivery method for existing therapeutic molecules not only improves the efficacy and safety of the medication, but also significantly improves patient compliance and the overall therapeutic benefit (6). Such dosage formulations have been created and changed more recently in order to maximize the permeability of the skin and the driving force behind drug diffusion (thermodynamic activity).

These methods make use of liposomes, other vesicles, pro-drugs, hyaluronic acid, supersaturated systems, and penetration enhancers. Transdermal delivery has an advantage over injectables and oral approaches by increasing patient compliance and removing first pass metabolism. Transdermal delivery eliminates pulsed systemic circulation for medications with short biological half-lives, which frequently results in unfavourable side effects, and permits continuous, controlled drug administration. Thus, several novel drug delivery methods exist, including transdermal drug delivery, controlled release, and transmucosal methods.
Transdermal drug delivery systems' primary goal is to deliver medications into the body's circulation through the skin at a set pace with little inter- and intrapatient fluctuation. 3 Currently, one of the most promising approaches to administering drugs is transdermal administration. 6 It lessens the burden that taking medication orally frequently places on the liver and digestive system. It improves patient compliance, reduces negative drug side effects brought on by transient overdoses, and is convenient for transdermal treatments that only need a single weak application



THE BENEFITS OF TDDS

1. Avoids first-pass hepatic metabolism
2. Keeps blood levels stable for a longer length of time.
3. Boost bioavailability.
4. Reduce the dosage to be given.
5. Reduce undesirable or adverse effects.
6. Reduce the likelihood of gastrointestinal side effects.
7. It is simple to cease in the event of harmful consequences. Improve patient compliance.
8. The frequency of dosing can be lowered.
9. Because of enhanced bioavailability, drug concentration can be lowered.
10. The first pass metabolism by the liver can be avoided.
11. They can help to avoid gastrointestinal medicine absorption problems caused by stomach pH, enzymatic activity, and drug interactions with food, drink, and other orally taken drugs.
12. Lower medication plasma concentrations, resulting in fewer adverse effects.
13. Because they are non-invasive, they eliminate the trouble of parenteral treatment.
14. They increased compliance compared to earlier dosage forms that needed more frequent dose administration since they provided prolonged treatment with a single application.
15. Drug therapy can be stopped quickly by removing the application from the skin's surface.
16. Self-administration is possible with these systems.
17. It decreases systemic drug interactions
18. It has a longer duration of action.

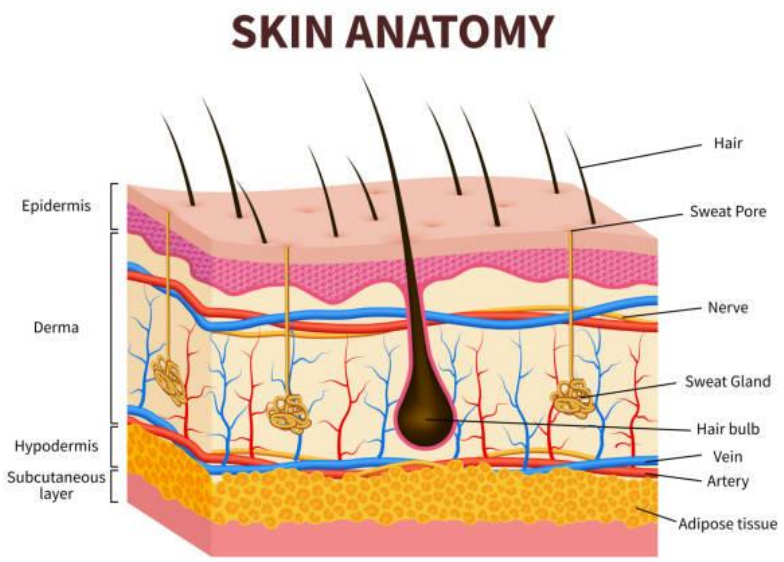
DISADVANTAGES OF TDDS

1. The price is high.
2. TDDS cannot deliver ionic medicines.
3. TDDS cannot reach high medication levels in blood/plasma.
4. It is not possible to create TDDS for medications with high molecular sizes.
5. TDDS cannot distribute medications in a pulsatile mode.
6. No TDDS can be developed if the medicine or formulation causes skin irritation.
7. Skin irritation may occur in some patients at the site of application
8. This system is uneconomic
9. Binding of the drug to the skin may cause dose dumping
10. It can be used only for chronic conditions, not acute conditions, because chronic conditions require drug therapy for a long period of time, such as hypertension, angina, and diabetes, etc.
11. Cutaneous metabolism can have an impact on the therapeutic effectiveness of a medication.
12. Ionic medicines are not appropriate for transdermal treatment.

13. Suitable for drugs with a lower molecular weight, i.e. less than 500 Dalton
14. Limited skin permeability
15. Limited to powerful medications
16. Not suited for big molecules (above 500 Daltons)
17. Skin adhesion of the patch
18. Drug breakdown in the skin
19. Drugs that are extremely melting cannot be administered using this method because to their limited solubility in both water and fat
20. Not suited if they cause skin sensitivity Ionic medicines cannot be delivered by this mechanism.

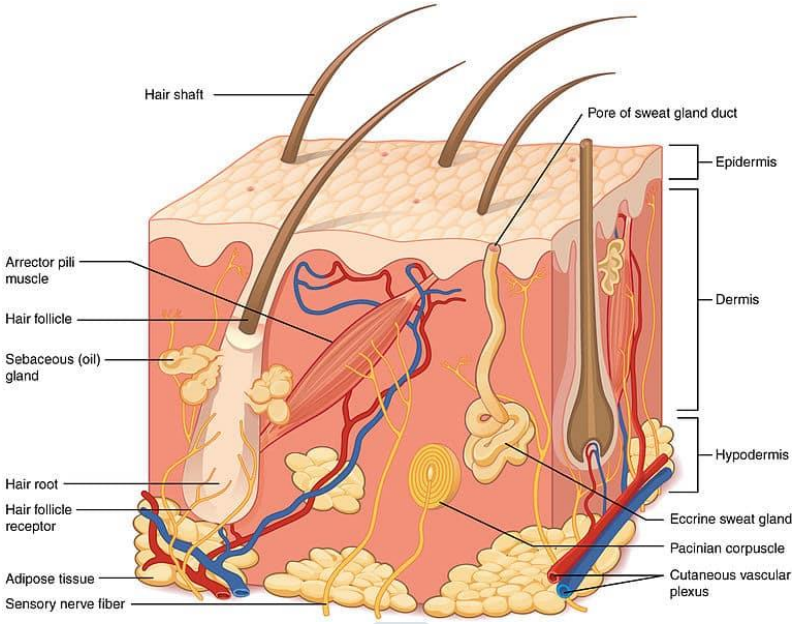
Anatomy and physiology of skin :-

Human skin is made up of three different yet interdependent tissues .
The stratified, vascular, cellular epidermis, the underlying dermis of connective tissues, and the hypodermis.



The epidermis

is a constantly self-renewing, stratified squamous epithelium that covers the entire outer surface of the body and is primarily composed of two parts: living or viable cells of the malpighian layer (viable epidermis) and dead cells of the stratum corneum, also known as the horny layer.
Viable epidermis is further categorized into four separate layers, as indicated in Fig. 2 12 Stratum lucidum Stratum granulosum Stratum spinosum Stratum basale.



Stratum corneum (Horney layer)

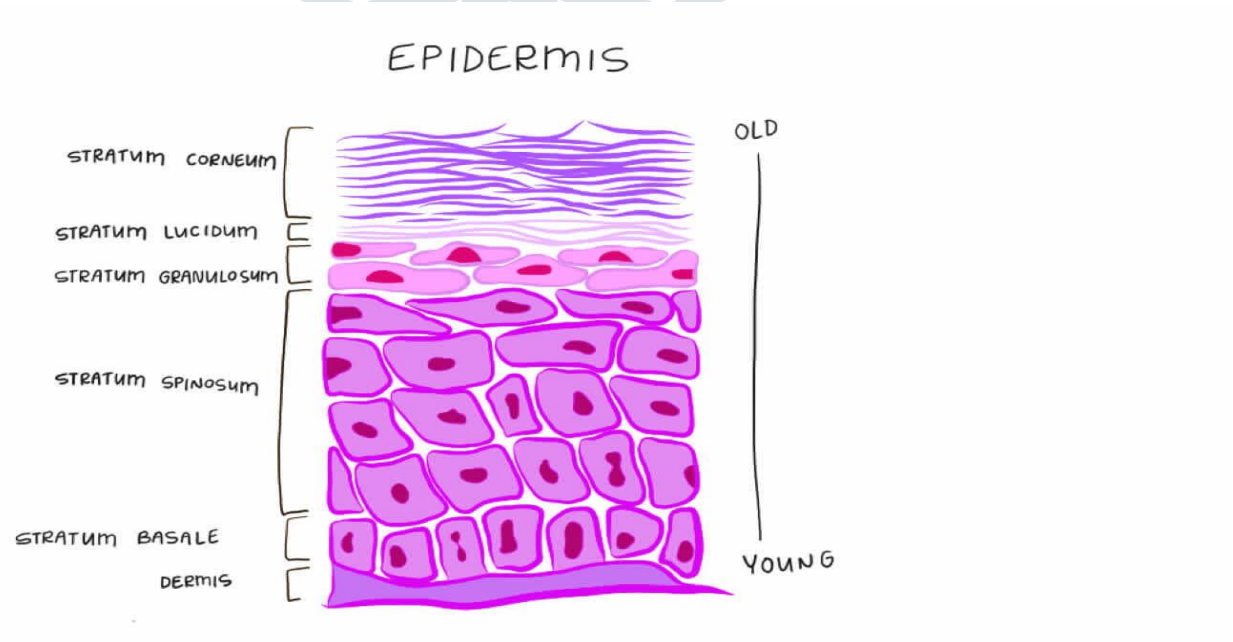
This is the outermost layer of skin, commonly known as the Horney layer. It is roughly 10 m thick when dry, but expands to many times that thickness when completely hydrated.

It has 10 to 30 layers of corneocytes, which are dead, keratinized cells. Drug molecules can enter the stratum corneum in one of three ways. The drug can be absorbed via the skin in a number of ways depending on the physicochemical properties of the medication.

Different absorption mechanisms are used for drugs that are both hydrophilic and lipophilic.

• Transcellular route • Intercellular route • Trans follicular route

Viable epidermis:- The thickness of this layer, which lies beneath the stratum corneum, ranges from 0.06 mm on the eyelids to 0.8 mm on the palms. It is made up of different layers as it moves inward, including the stratum basale, stratum lucidum, stratum granulosum, and stratum spinosum. The epidermis is constantly renewed by cell division in the basal layer, which makes up for the loss of horny, dead skin cells from the skin's surface. The basale layer's cells produce the stratum corneum's outermost layer, which is formed when they travel outward and undergo morphological and histochemical changes.



Dermis The dermis is a 3 to 5 mm thick layer made up of a connective tissue matrix that houses nerves, blood vessels, and lymphatic vessels. The cutaneous blood supply is crucial for maintaining body temperature. It provides the skin with nutrition and oxygen while eliminating impurities and waste. Capillaries, which are 0.2 mm below the skin's surface, are where the majority of molecules that cross the skin barrier sink. The resulting concentration gradient across the epidermis, which results from the blood supply maintaining a very low dermal concentration of a permeant, is essential for transdermal penetration.
Hypodermis The dermis and epidermis are supported by the hypodermis, or subcutaneous fat tissue. It functions as a place to store fat. This layer offers nutrient support, mechanical protection, and aids in temperature regulation. Principal blood arteries, nerves, and possibly pressure-sensing organs are carried there to the skin.
For transdermal drug administration, the medication must pass through all three of these layers and enter the bloodstream, whereas for topical drug delivery, just stratum corneum penetration is necessary, and the drug should then be retained in the skin layers.

Types of transdermal patches :-

- *Single-layer drug-in-adhesive.*
- *Multi-layer drug-in-adhesive*
- *Reservoir*
- *Matrix.*
- *Vapour patch*

Drug-in-Adhesive with a single layer :-

The fact that the medication is integrated directly into the skin-contacting adhesive distinguishes it. The adhesive also serves as the foundation for the formulation in this transdermal system design, retaining the drug and all excipients in one backing film while also acting as a means of fastening the system to the skin. How quickly the drug diffuses through the skin affects how quickly this type of system releases medication.

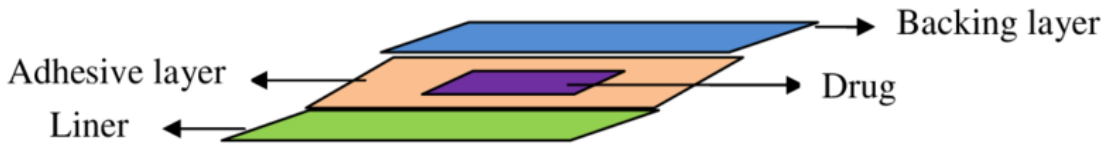
The Multi-layer Drug-in-Adhesive:-

In that the medicine is incorporated directly into the adhesive, it is comparable to the Single-layer medicine-in-Adhesive. The term "multi-layer" describes the inclusion of a membrane or several drug-in-adhesive layers underneath a single backing film in between two different drug-in-adhesive layers.

Reservoir :-

Its main distinguishing feature is the presence of a liquid compartment containing a medication solution or suspension that is separated from the release liner by an adhesive and semi-permeable membrane. The

adhesive part of the product that attaches to the skin might be either a continuous layer between the membrane and the release liner or a concentric design all around the membrane.



Drug Matrix-in-Adhesive
The presence of a semisolid matrix containing a medication solution or suspension that is in direct touch with the release liner distinguishes it from other formulations. The element causing skin adherence is built into an overlay and arranges itself in a concentric pattern all around the semisolid matrix.

Vapour patch
This kind of patch uses an adhesive layer to release vapour in addition to holding the other layers together. New on the market, vapour patches release essential oils for up to 6 hours. Vapour patches, which release essential oils for up to 6 hours, are just now beginning to appear on the market. The vapour patches release essential oils and are mostly used to treat decongestion cases. Alternatives include controller vapour patches, which improve the quality of sleep. Additionally, there are vapour patches available that can reduce a person's monthly cigarette use. There are also months on the market.

Components of TDDS :-

The major components of a transdermal patch are:

Release Liner :- safeguards the patch while it is stored. The liner is taken out before usage

Drug reservoir :- The drug reservoir is the most crucial element of TDDS. There are drug particles in the matrix that have been dissolved or scattered.
To render the medication soluble, a variety of solvents and cosolvents are utilized. When making a selection, the impact of the solvent and cosolvent should be taken into account.

Adhesive :-
enables both the skin and the patch's component elements to be attached to the skin. For the TDDS to stay in place for a long time, the glue needs to have strong enough adhesion properties. For transdermal patches, pressure-sensitive adhesives are frequently utilized to keep the skin in place. Silicone adhesives, polyisobutylene adhesives, and poly acrylate-based adhesives are frequently used adhesives.

Membrane :-
The medicine is released from the reservoir and multi-layer patches under the control of the membrane. It might or might not have membrane that controls flow rate. It should be flexible enough to bend or stretch without splitting or cracking. Polyethylene sheets, ethylene vinyl acetate copolymer, and cellulose acetat are a few examples of rate-controlling membranes.

Backing :-
protects the patch from the environment. Drugs and penetration boosters shouldn't be able to pass through the backing layer. It holds the complete system and shields the drug reservoir from the atmosphere. Polyesters, aluminized polyethylene terephthalate, and siliconized polyethylene terephthalate are the most often utilized backing materials

Various methods for preparation of transdermal drug delivery system:-

Asymmetric TPX membrane method: A heat sealable polyester film (type 1009, 3m) with a backing membrane concave of 1 cm in diameter can be utilized to create a prototype patch. A poly (4methyl-1-pentene) asymmetric membrane made of TPX is used to cover the concave membrane, which is then sealed with an adhesive.

Asymmetric TPX membrane preparation :- The dry/wet inversion procedure is used to make them. To create a polymer solution, TPX is dissolved in cyclohexane, a solvent, and nonsolvent additives. Using a garden knife, the polymer solution is cast onto a glass plate at a predetermined thickness after being held at 40°C for 24 hours.
The casting film is then evaporated at 50°C for 30 seconds, after which the glass plate must be submerged immediately in the coagulation bath (which must be kept at 25°C). The membrane can be removed after 10 minutes of immersion and allowed to air dry for 12 hours in a circulation oven at 50°C.

Circular teflon mould method :- Solutions with different ratios of polymers are utilized in an organic solvent. Half as much of the same organic solvent is used to dissolve the calculated amount of medication. The second half of the organic solvent is used to dissolve enhancers at various concentrations before they are applied. The plasticizer di-Nbutylphthalate is included in the drug polymer solution. The entire mixture must be stirred for 12 hours before being placed into a circular Teflon mold. A flat surface is used to position the molds, and an inverted funnel is used to cover them to In a laminar flow hood model, regulate the vaporization of the solvent by adjusting the air speed to 0.5 m/sec. 24 hours are given for the solvent to evaporate. To counteract the effects of aging, the dried films must be kept for a further 24 hours at 250.5 °C in a desiccator containing silica gel before examination. Within a week after their preparation, these films must be appraised.

Mercury substrate method :- This approach involves dissolving the medication and plasticizer in a polymer solution. The aforementioned solution should be agitated for 10 to 15 minutes to create a homogenous dispersion before being placed onto a mercury surface that has been leveled. After that, an inverted funnel is placed over the solution to prevent solvent evaporation.

By using "IPM membranes" method: According to this procedure, the medication is dissolved in a solution of water and propylene glycol that also contains carbomer 940 polymer, and it is then agitated for 12 hours in a magnetic stirrer. Triethanolamine is to be added in order to neutralize the dispersion and make it viscous. If the drug's solubility in aqueous solution is particularly poor, buffer pH 7.4 can be employed to create solution gel. The IPM membrane will incorporate the produced gel.

By using "EVAC membranes" method :- In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol, carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

Aluminium backed adhesive film method: In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol, carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custammade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

Preparation of TDDS by using proliposomes: The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 1:2 can be used as an optimized ratio. The proliposomes are prepared by taking 5mg of mannitol powder in a 100ml round bottom flask which is kept at 60-70 °C temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 min. After drying, the temperature of the water bath is adjusted to 20- 30 °C. Drug and lecithin are dissolved in a suitable organic solvent mixture. Aliquot of 0.5 ml of the organic solution is introduced into the round bottomed flask at 37 °C After the entire drying process, a second aliquot (0.5ml) of the solution containing mannitol should be added.

The flask containing the proliposomes is attached to a lyophilizer after the final loading, and the drug-loaded mannitol powders (proliposomes) are then left in desiccators overnight before being sieved through a 100 mesh screen. When ready for characterisation, the collected powder is transferred to a glass bottle and kept at freezing temperatures.

By using free film method: Casting on the surface of the mercury creates a free film of cellulose acetate. 2% weight-to-weight polymer solution is made using chloroform. Plasticizers are included at a 40% weight-to-weight (w/w) concentration in the polymer. In a glass petri dish with mercury on the surface, five ml of polymer solution was added to a glass ring. Placing an inverted funnel over the petridish regulates the solvent's rate of evaporation. After the solvent has completely evaporated, the mercury surface is observed to detect the film formation. Before usage, the dried film will be sorted out and kept in desiccators between wax paper sheets. The volume of the polymer solution can be changed to create free films of various thicknesses.

EVALUATION PARAMETERS :-

1. Interaction studies
2. Thickness of the patch
3. Weight uniformity
4. Folding endurance
5. Percentage Moisture content
6. Percentage Moisture uptake
7. Water vapour permeability (WVP) evaluation
8. Drug content
9. Uniformity of dosage unit test
10. Polariscope examination
11. Shear Adhesion test
12. Peel Adhesion test
13. Thumb tack test
14. Flatness test
15. Percentage Elongation break test
16. Rolling ball tack test
17. Quick Stick (peel-tack) test
18. Probe Tack test
19. In vitro drug release studies
20. In vitro skin permeation studies
21. Skin Irritation study

FACTORS AFFECTING TRANSDERMAL PERMEABILITY :-

The main method of transport across mammalian skin is passive diffusion, either initially non-steady state through the transappendageal route or the transepidermal route at steady state. The following categories describe the elements that primarily affect the stratum corneum of the skin's permeability

1. Physicochemical properties of the penetrant.
2. Physicochemical properties of the drug delivery system.
3. Physicochemical and pathological conditions of the skin

Physicochemical properties of the penetrant molecule :-

Drugs with both lipid and water solubilities are more readily absorbed via the skin, according to the *partition co-efficient.*

The partition co-efficient has a linear relationship with the transdermal permeability co-efficient. Changes to the vehicle may also impact a drug's lipid/water partition coefficient molecule. Chemical alteration of a drug's molecule can change its partition coefficient without changing the drug's pharmacological activity.

pH level: Acidic and basic medications' rates of absorption are primarily affected by pH, and pharmaceuticals in their unmodified form have greater penetration power. Strong pH dependence is seen in the transport of ionizable species from aqueous solutions.

Drug concentration

Mammalian skin transdermal permeability is a passive diffusion process that is dependent on the concentration of penetrant molecules on the skin's surface layer.

Physicochemical properties of the drug delivery system :-

a. *The affinity of the vehicle for the drug molecules* :- It may affect how the medication molecule leaves the delivery system. The drug's release rate will depend on how soluble it is in the vehicle. The drug's suspension or dissolution in the delivery system and the drug's interfacial partition co-efficient from the delivery system to epidermal tissue determine the mechanism of drug release.

b. *Composition of drug delivery system*:- The composition of the drug delivery system may have an impact on the stratum corneum's permeability through hydration in addition to the rate of drug release.

c. *Enhancement of transdermal permeation*:- Because the stratum corneum is dead, there is less medication release from the dose form. Drug penetration into the skin is increased via penetration enhancers, which alter the stratum corneum's physicochemical or physiological composition. Several chemicals have been discovered to have properties that enhance medication penetration.

Physiological and pathological condition of the skin :-

Age of the skin:-

Infant and fetal skin seems to be more porous than adult skin. Children absorb topical steroids via the skin more quickly than adults do. According to studies, water permeability is the same in both adults and children.

Lipid film :- The sebaceous glands and cell lipids like sebum excrete the lipid layer on the skin's surface. and epidermal cells that contain emulsifying agents may offer a protective film to stop the loss of the skin's natural moisturizing component and aid in preserving the stratum corneum's barrier function.

Skin hydration :- The stratum corneum can become more permeable by being hydrated. When the tissue were hydrated, the rate of penetration of the most water soluble esters increased more than that of the other esters when salicylic acid penetration through skin with dry and hydrated corneum was assessed.

Skin temperature :- The rate at which skin permeation occurs increases as skin temperature rises. An increase in skin temperature may also cause blood vessels that are in contact with the skin to dilate more, which would increase percutaneous absorption.

Cutaneous drug metabolism :- Due to the presence of metabolic enzymes in the epidermal layers, part of the medicine that has passed the stratum corneum barrier enters the general circulation in an active form, while some of it does so in an inactive or metabolic form. According to reports, more than 95% of the testosterone that was absorbed was digested as it entered the body through the skin.

Species differences :- Mammalian skin from different species has significant anatomical variations in aspects such stratum corneum thickness, number of sweat glands, and hair follicles per unit surface area.

Pathological injury to the skin:- Skin damage can result in disruption of the stratum corneum's continuity and an increase in skin permeability

Transdermal drug delivery systems have following advantages over conventional drug delivery.

1. They can prevent issues with drug absorption in the gastrointestinal tract brought on by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally taken medications.
2. They can replace oral medication administration when it is inappropriate, such as when vomiting or diarrhea occur.
3. They avoid liver enzymes deactivating the medication and first-pass metabolism.
4. They are non-invasive, therefore parenteral therapy's drawbacks are avoided.
5. Compared to other dosage forms, they offer longer therapy with a single application, enhancing compliance and requiring fewer dose administrations overall.
6. Transdermal drug delivery systems may be removed from the skin's surface to quickly end medication administration.
7. Due to their physical presence, distinguishing traits, and identifying markers, they are quickly and easily recognized in crises (such as an unresponsive, unconscious, or comatose patient).

Some of the applications of transdermal drug delivery system (TDDS) are:-

- The nicotine patch, which distributes nicotine in controlled dosages to aid in quitting smoking, is the most popular transdermal patch in the United States of America. In Europe, the first vaping patch for quitting smoking was authorized in 2007.
- Two opioid drugs, fentanyl CII (marketed as Duragesic) and buprenorphine CIII (marketed as BuTrans), are frequently used in patch form to treat chronic pain.
- Hormonal patches: Oestrogen patches, a type of hormone replacement treatment, are sometimes recommended to transgender women and to treat menopausal symptoms (as well as postmenopausal osteoporosis).
- Testosterone CIII patches for both males (Androderm) and women (Intrinsa) and contraceptive patches (marketed as Ortho Evra or Evra).

- Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills

- TDDS can be used to deliver drugs that are unstable in the gastrointestinal tract or are extensively metabolized by the liver, such as peptides, proteins, hormones, and vaccines1.

- TDDS can be used to treat chronic conditions that require long-term therapy, such as hypertension, angina, diabetes, pain, and hormone replacement12.

- TDDS can be used to deliver drugs that have a narrow therapeutic window or exhibit dose-dependent side effects, such as antiarrhythmics, anticoagulants, and opioids12.

- TDDS can be used to deliver drugs that have poor oral bioavailability due to low solubility or permeability, such as fentanyl, estradiol, and nicotine12.

- TDDS can be used to deliver drugs that have a short biological half-life or require frequent dosing, such as nitroglycerin, clonidine, and scopolamine12.

- TDDS can be used to deliver drugs that have a local effect on the skin or underlying tissues, such as anti-inflammatory agents, antifungal agents, and local anesthetics12.

- TDDS can be used to deliver drugs that have a cosmetic or aesthetic purpose, such as skin whitening agents, anti-aging agents, and hair growth stimulants12.

Conclusion :-

The review paper on transdermal drug delivery systems (TDDS) provide helpful information on TDDS and its evaluation process as a convenient resource for research scientists working on TDDS. Given that they can be employed to produce prospective deliverable pharmaceuticals from both hydrophobic and hydrophilic active molecules, the information above suggests that TDDS have great potentials. s beneficial for the drug's local and topical actions. The best candidates for TDDS are medicines that have a hepatic first pass action and are unstable in GI circumstances. To optimize this drug delivery technique, more understanding of the numerous biological interactions and polymer processes is required. The TDDS, the subsequent generation of drug delivery systems, has a real-world application.

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