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A REVIEW ON: TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

The oral route is the most often used method of medication delivery. This method of administration has certain noteworthy benefits but also some serious disadvantages, such as first pass metabolism, medication degradation in the gastrointestinal system as a result of an enzyme, PH, etc. To get around these problems, a novel medication delivery mechanism was created. Recent research has demonstrated that the skin is a helpful pathway for delivering medications to the bloodstream. Transdermal medication delivery systems have gained a lot of attention because of their ability to control drug release and their non-invasive design. This review's objective is to provide a concise summary of advancements, challenges, and possible uses. The article discusses the variety of techniques used to increase skin penetration, including formulation strategies and innovative drug delivery techniques. Additionally, it highlights how transdermal drug administration techniques can improve therapeutic results, reduce side effects, and increase patient compliance. Additionally, the analysis highlights the limitations and difficulties associated with transdermal drug delivery, such as the characteristics of skin barriers, drug characteristics, and regulatory considerations. The evaluation also offers details about potential future research and development opportunities to overcome the present difficulties and improve the drug.

Introduction

Transdermal drug delivery devices, or "patches," are another name for dosage forms. A therapeutically effective dosage of the medication is applied throughout the patient's skin thanks to careful design.Transdermal medication administration has proven to be superior than injectables and oral methods due to its ability to improve patient compliance and avoid first pass metabolism.[1]Transdermal patches: are the dosage forms made to enter the bloodstream from the outside of the skin through its layers and administer a therapeutically effective amount of medication. Transdermal patches are extensively utilised for topical, cosmetic, and transdermal medication delivery. These patches are the result of advancements in skin science, technology, and knowledge that have been made possible by trial and error, clinical observation, evidence-based research, and records that go back to the earliest known human records. These reviews outline the history of topical distribution from the first topical treatments to the current generation of transdermal patches and their active ingredients. The examination of the various patch designs, their limitations, and the specifications for the actives to be employed for transdermal delivery come next. Next, characteristics of currently marketed products are discussed, including their safety, regulatory aspect, and variability. The review ends with a look at potential developments for transdermal patches and drug delivery systems in the future, including the use of patches in conjunction with active delivery systems, minimally invasive microneedle patches, and cutaneous solutions like metered-dose systems. [2]At present, different transdermal drugs are used for various diseases such as hyoscin for motion sickness, nitro-glycerine, and clonidine used for cardiovascular disease and fentanyl used for chronic pain. This system having several advantages and disadvantages. [16]

Definition:

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. [5]

ADVANTAGES OF TDDS

- The first pass effect is circumvented via transdermal medication delivery devices.
- Increases the bioavailability.
- lowers the frequency of dose.
- Self-administration is achievable with the transdermal medication delivery method.
- The intestinal fluids and stomach acid are not hampered by the transdermal drug delivery technology.
- For individuals who are unable to take oral dosage forms, there is an alternative method of administration called the transdermal system.
- The transdermal drug delivery device can be used with patients who are unconscious or experiencing nausea.
- Transdermal drug administration is a great fit for medications with stable plasma levels.
- It keeps blood levels regulated, steady, and consistent for an extended amount of time.
- Compared to other traditional therapy, a lower daily dose of the medication is necessary.
- The application of a patch to the skin's surface can end a drug regimen. [3]

DISADVANTAGES OF TDDS

- At the location where the patch is applied, some patients experience contact dermatitis caused by one or more system components.
- Higher cost compared to the oral formulation.
- Not suitable for the ionic drug.
- It may cause allergic reactions.
- The skin's barrier function varies with age and from person to person in the same person.
- The molecular weight of less than 500 Da is essential.
- Permeation through the skin requires a log p (octanol/water) of between 1 and 3, sufficient lipid, and aqueous solubility.
- Transdermal administration is only appropriate for potent medications.
- It is unable to provide a pulsatile administration of the medication from the dose form.[3]

ANATOMY PHYSIOLOGY OF THE SKIN:

The human body's skin covers about 2 square metres of surface area. It acts as a permeability barrier to prevent the transdermal absorption of several chemical and biological substances. The human skin is mostly composed of three layers.

1. Epidermis
2. Dermis
3. Hypodermis

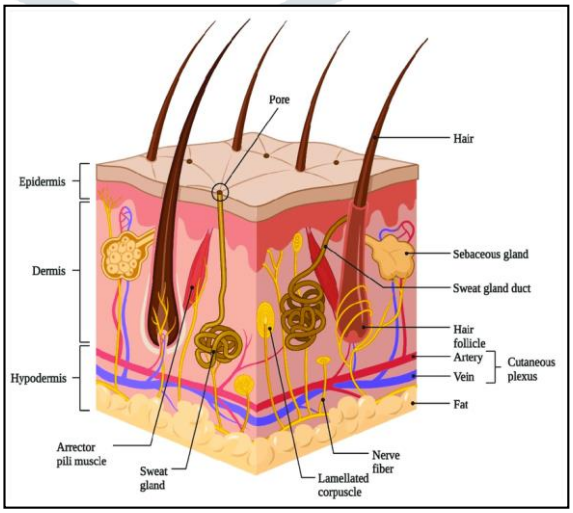

Figure no.1: transvers section of human skin [3]

Epidermis

The thickness of the multilayer epidermis varies from 0.8 mm on the palms and soles to 0.6 mm on the eyelids, depending on the size and quantity of cells in the layers. Conium stratum. The word "horny layer" refers to the outermost layer of skin. When completely hydrated, it swells to several times its dry thickness of around 10 mm. It is made up of 10–25 layers of corneocytes, which are dead, keratinized cells. Although flexible, it is not very porous. One of the main obstacles to the drug's entry is this stratum cornium. It is possible to model the architecture of the horny layer as a wall-like structure. The keratinized cells in this model serve as proteins "bricks" embedded in lipid "mortar" The lipids are organised into several bilayers. The lipid fraction contains enough amphipilic material, including cholesterol and polar free fatty acids, to sustain a bilayer structure. [5]

The viable epidermis is divided into the four distinct layers such as:

1. Stratum corneum
2. Stratum granulosum
3. Stratum spinosum
4. Stratum basale.[16]

Dermis

The layer of skin directly beneath the epidermis is called the dermis, and it is 3 to 5 mm thick. It is composed of a matrix of connective tissues that includes blood vessels, lymphatic vessels, and nerves. The cutaneous blood supply plays a vital function in controlling body temperature. It provides the skin with nourishment and oxygen in addition to getting rid of waste and contaminants. Capillaries, which extend to within 0.2 mm of the skin's surface, are where most molecules that breach the skin barrier find a sink state. Thus, the dermal concentration of permeate is kept at a very low level by the blood supply. The resulting concentration differential across the epidermis is the key factor that propels transdermal penetration. When it comes to applying transdermal medicine, this layer. [4]

Hypodermis

The dermis and epidermis are supported by the hypodermis, or subcutaneous tissue. It acts as a place to store fat. The hypodermis layer offers mechanical protection, nutritional support, and temperature regulation. [4] The hypodermis, or subcutaneous fat tissue, supports the dermis and epidermis. It serves as a repository for fat. This layer provides nutritional support, mechanical protection, and help with temperature regulation. It carries primary blood vessels, nerves, and maybe sensory pressure organs to the skin. While only the stratum corneum needs to pass through for topical drug administration in order for the drug to be retained in the skin layers, transdermal drug delivery requires the medication to pass through all three of these layers in order for it to enter the bloodstream. [5].

Ideal characteristics of drug for transdermal drug delivery system

- Shelf life :Up to 2 year
- Patch size :< 40 cm2
- Dose frequency :Once a daily to once a week Aesthetic appeal Clear, tan or white color
- Packaging :Easy removal of release liner and minimum number of steps required to apply Skin reaction Non irritating and non sensitizing.
- Release :Consistent pharmacokinetic and pharmacodynamic profiles over time.[24]

Sr.no	Parameters	Properties
1.	Molecular weight	<500
2.	Dose	Less than 20 mg/day
3.	Half -life	10 or less (hr)
4.	Partition coefficient	Log p (1-4)
5.	Skin permeability coefficient	$>0.5*10^{-3}$ cm/h
6.	Oral bioavailability	Low
7.	Melting point	$<200^{0}$c
8.	Therapeutic index	Low
9.	Lipophilicity	10<ko/w<1000
10.	PH	5-9

Table no 1. Ideal properties of TDDS [3]

COMPONENTS OF A TRANSDERMAL PATCH :

Transdermal patch may consist of the following components:

1. Liner: This shields the patch while it's being stored. It is taken out before usage.
2. Drug: Direct contact exists between the drug solution and the released.
3. Adhesives: These are used to attach the patch to the skin and to bind the patch's components together.
4. Membrane: This device regulates the drug's release from multi-layer patches and reservoirs.
5. Backing: This shields the patch from the external environment.[1]

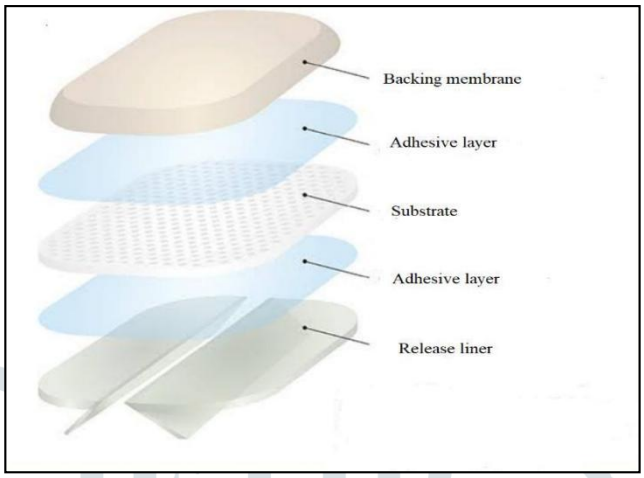

Figure no.2 : composition of transdermal patch [3]

- **Basic Components of Transdermal Drug Delivery Systems:**

A. Polymer matrix or matrices.
B. The drug
C. Permeation enhancers
D. Other excipients

A. Polymer Matrix:

An essential component of the transdermal medication delivery system is polymer. Numerous polymeric material types have been used to achieve rate-controlled medicine administration. The drug release mechanism is determined by the dig's physicochemical properties and the polymer utilised in the device's fabrication. A polymer has to fulfil certain characteristics in order to be used in a transdermal system.

The transdermal medication delivery system requires polymer, which is an essential component. Many kinds of polymeric materials have been used to achieve rate-controlled drug delivery. The drug release mechanism of the device is determined by the physicochemical properties of the polymer and dig. employed in its fabrication. The following conditions must be satisfied by a polymer before it may be used in a transdermal system.[19]

NATURAL POLYMER	SYNTHETIC ELASTOMER	SYTHETIC POLYMER
Gelatin	Neoprene	Polyetylene
Gum Arabic	Silicon Rubber	Polystyrene
Starch	Butyl Rubber	PVC
Shellac	Chloroprene	PVP
Zein	Polysiloxane	Polyster

Table no.2: Polymer Matrix

The drug's release from the device is regulated by the polymer. The following polymers could be helpful for transdermal devices:

a) Natural Polymers: e.g., cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

b) Synthetic Elastomers: e.g., polybutadieine, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.

c) Synthetic Polymers: e.g., polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide,Polyurea, Polyvinyl pyrrolidone, Polymethylmethacrylate, Epoxy etc[6].

B. Drug:

The medicine must be carefully chosen in order to build a transdermal drug delivery system that works. Some of the desired characteristics of a medication for transdermal distribution are listed below.

Physical and chemical characteristics: The medication ought to be soluble in both hydrophilic and lipophilic phases, with a molecular weight of no more than 1000 Daltons. Transdermal drug administration is incompatible with severe partitioning properties. The medicine should also not irritate in addition to being strong, having a short half-life, and having a low melting point. The medication ought to be soluble in both hydrophilic and lipophilic phases, with a molecular weight of no more than 1000 Daltons. Transdermal drug administration is incompatible with severe partitioning properties. The medication should also not irritate in addition to being strong, having a short half-life, and having a low melting point.[6]

C. Enhancers of Permeation:

These are substances that increase the permeability of the skin by changing the skin's ability to act as a barrier to the flow of a desired penetrant.These can easily be categorized under the principal headings that follow:

1. **Solvents:**

These compounds increase penetration, particularly when the polar component is absorbed via a fluidized lipid pathway contain water alcohols like methanol and ethanol as an example; dimethyl sulfoxide is an alkyl methyl sulfoxide. N-methyl, 2-purrolidone, and 2-pyrrolidone are the alkyl equivalents of dimethyl sulfoxide pyrrolid-containing acetamide and dimethyl formamide ones. Other solvents, silicone fluids, glycerol, and propylene glycol isopropyl palmitate are as well as Azone (laurocaprofen). .

2. **Surfactants:**

It has been proposed that these compounds facilitate the flow of polar routes, especially those using hydrophilic medicines. The ability of the surfactant to change penetration is the polar head's function. group as well as the hydrocarbon chain's length. Dioctyl sulpho-succinate, sodium lauric acid, and decodecyl—such as methyl sulfuroxide—are examples of anionic surfactants. Unique surfactants include Pluronic F68 and F127, as well as Bile salts such sodium deoxycholate, sodium taurocholate, and sodium tauroglycocholate. Binary system: These appear to be systems that are open. along the uninterrupted routes as well as the varied multilaminate route. like Propylene glycol, oleic acid, and 1, 4-butane diol.[6]

3. **Other chemicals:**

One of them is urea. keratolytic and moisturising agent; calcium thioglycolate ergic compounds; N, N-dimethyl-anticholin-m-toluamide. A potential infiltration Despite the latest reports, there is little information available on enhancers. Among them are soyabean casein, di-o-methyl-B-cyclodextrin, and eucalyptol.[6]

D. Other excipients :

1. Adhesives:

Thus far, every transdermal device has been attached to the skin by the use of a pressure-sensitive adhesive that may be applied to the device's face, back, and peripheral regions. The following requirements should be met by both adhesive systems:

- Should adhere to the skin aggressively, should be easily removed.
- Should not leave an unwashable residue on the skin.
- Should not irritate or sensitize the skin.

The face adhesive system should also fulfill the following criteria;

- Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.

- Permeation of drug should not be affected.
- The delivery of simple or blended permeation enhancers should not be affected.

2. Backing membrane:

Because they are flexible, backing membranes allow printing, offer a strong attachment to the drug reservoir, and keep the drug from escaping the dose form via the upper opening. Products like sticky foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc), plastic backing with absorbent pad and occlusive base plate (aluminium foil), metallic plastic laminate, etc. are shielded from skin contact by an impermeable material. .[6]

Conditions in which transdermal patches are used :

1. When the patients are unable to take oral medicine and have intolerable side effects (including constipation).
2. When a patients are nauseated or unconscious.
3. It can be used in combination with other enhancement strategies to produce synergetic effects for treatment.[3]

TYPES OF TRANSDERMAL PATCHES

1. Single-layer Drug-in-Adhesive:

This method also provides the medication in the sticky layer. The sticky layer facilitates both the release of medication and the attachment of the several layers. The adhesive layer is surrounded by two additional layers: a temporary liner and a backing.

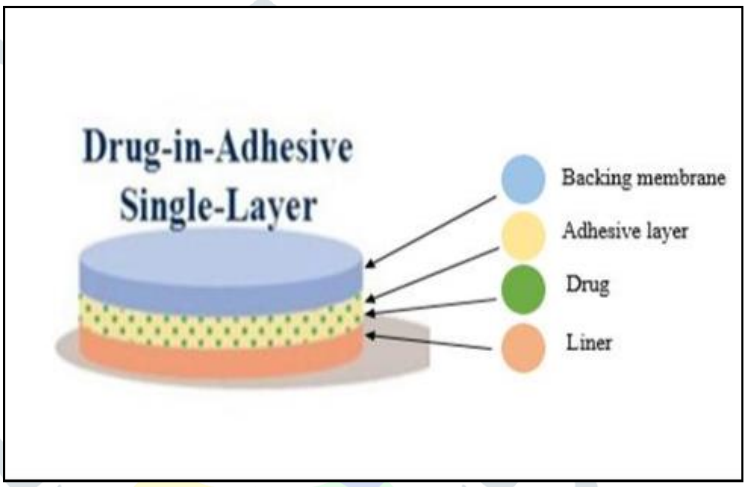

Figure no.3 : Single layer drug in the adhesive patch[3]

2. Multi-layer Drug-in-Adhesive:

Since both adhesive layers are in charge of the drug's release, the multilayer drug-in adhesive patch and single-layer systems are quite comparable. An additional layer of drug-in-adhesive, often divided by a membrane, is present in the multi-layer system (in many cases). This kind of patch also features a temporary liner layer connected to a permanent backing.

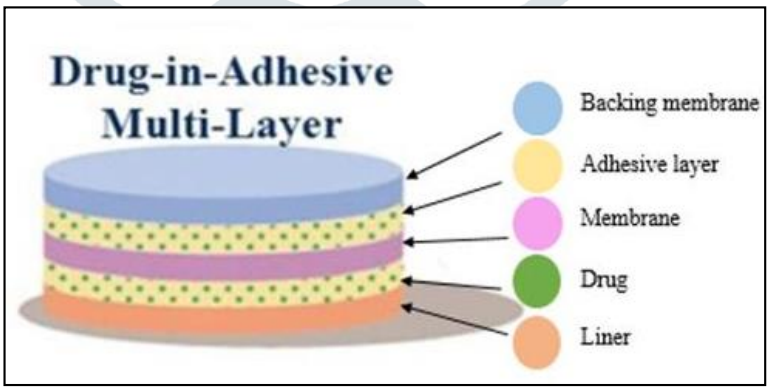

Figure no.4 Multi-layer Drug-in-Adhesive[3]

3. Drug Reservoir-In-Adhesive:

A distinct drug layer is present in the drug reservoir-in-adhesive system, in contrast to the single-layer and multi-layer drug-in adhesive systems. The sticky layer acts as a barrier between the drug layer and the drug solution or suspension.This patch also includes a backing layer. This kind of system follows zero order kinetics.

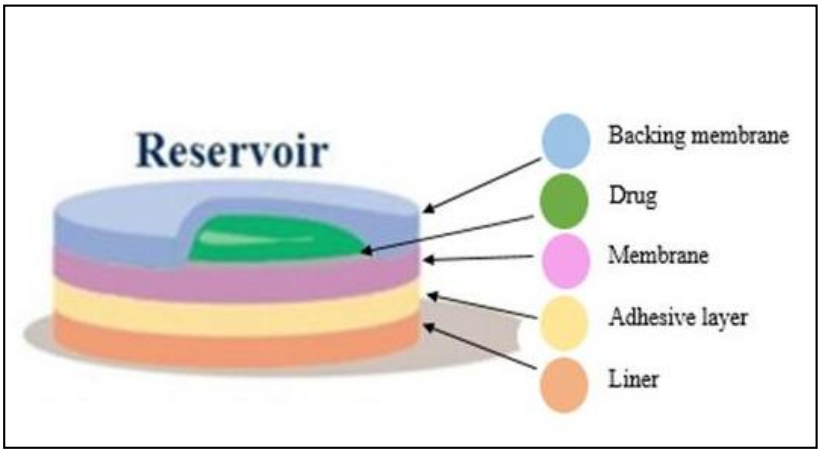

Figure no.5 Drug Reservoir-In-Adhesive[3]

4. Drug Matrix-In-Adhesive:

The Matrix system is connected to a drug layer in this kind of transdermal patch, which takes the shape of a semisolid matrix holding a medication solution or suspension. This patch has a layer of adhesive covering the medication layer to some extent.

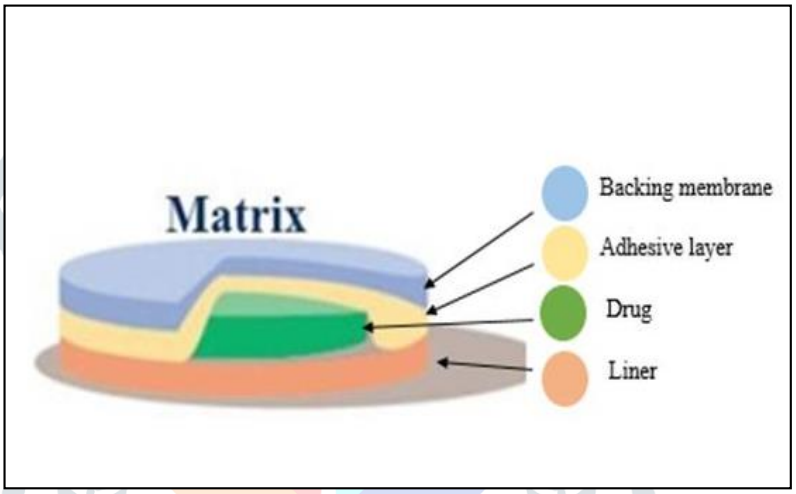

Figure no.6 Drug Matrix-In-Adhesive [3]

5. Vapour Patch:

The vapour patch essentially serves two purposes: it adheres the several layers together and releases vapour. Vapour patches are a relatively new product on the market. Because of their ability to release essential oils for up to six hours, they are mostly utilised for decongestion. There are also controller vapour patches available on the market that enhance sleep quality. Additionally, available on the market are vapour patches, which are necessary to cut back on the number of cigarettes. .[1]

VARIOUS METHODS FOR PREPARATION TDDS

1. Asymmetric TPX membrane method

A heat-sealable polyester film (type 1009, 3m) with a 1cm diameter concave can be utilised to manufacture a prototype patch. This film will serve as the backing membrane. The drug sample is injected into the concave membrane, sealed with an adhesive, and coated with an asymmetric membrane made of TPX poly (4-methyl-1-pentene).

2. Circular Teflon mould method

An organic solvent is used to dissolve solutions that include polymers in different ratios. 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 varying concentrations before adding them. To the drug polymer solution, di-N-butyl phthalate is added as a plasticizer. After 12 hours of stirring, the entire mixture should be put into a circular Teflon mould. To regulate solvent vaporisation in a laminar flow hood model with an air speed of 0.5 m/s, the moulds must be set on a flat surface and covered with an inverted funnel. For a whole day, the solvent is left to evaporate. Before evaluation, the dried films must be held for a further twenty-four hours at 25±0.5°C in a desiccator filled with silica gel to prevent ageing effects. Within a week following their preparation, the type films must be reviewed. [7]

3. By using IPM membranes method

Using a magnetic stirrer, the medication is dissolved in a solution of water and propylene glycol that contains carbomer 940 polymer, and the mixture is then shaken for a duration of 12 hours. Triethanolamine is to be added to the dispersion in order to neutralise it and make it viscous. If the drug's solubility in aqueous solution is extremely low, solution gel can be created using buffer pH 7.4. The IPM membrane will incorporate the gel that has produced. [7]

4. Mercury Substrate Method

In this procedure, the necessary quantity of medication is dissolved in a fixed volume of polymer solution together with plasticizer. The aforementioned solution should be mixed for a while to create a uniform dispersion, then left until all air bubbles are gone before being poured into a glass ring that is set over the mercury surface in a glass petri dish. An inverted funnel placed above the petri dish regulates the solvent's rate of evaporation. A desiccator is required for the storage of the dried films.

5. Glass Substrate Method

After allowing the polymeric solutions to expand, the necessary amount of plasticizer and medication solution are added, and everything is mixed for ten minutes. In order to remove any trapped air, it is also left aside for a while before being poured into a dry, clean anumbra Petri plate. To regulate the solvent evaporation rate, place a glass funnel upside-down over the Petri plate. The dried films are removed and kept in a desiccator after being left for the night.

6. By Using EVAC Membranes Method

Polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes, and 1 percent Carbopol reservoir gel can be utilised as rate control membranes to prepare the target transdermal therapeutic system. Gel is made with propylene glycol if the medication is not soluble in water. Propylene glycol is used to dissolve the drug; Carbopol resin is then added to the mixture and neutralised with a 5 percent w/w sodium hydroxide solution. The medication (in gel form) is applied to a backing layer sheet that covers the designated area. To create a leak-proof device, a rate-regulating membrane will be placed over the gel and the borders will be sealed with heat. .

7. Aluminium Backed Adhesive Film Method

If the loading dose for a transdermal drug delivery system is more than 10 mg, unstable matrices may be produced. The adhesive film approach with aluminium backing is appropriate. Since the majority of medications and adhesives are soluble in chloroform, it is the solvent of choice for preparing the same. Adhesive substance is added to the drug solution and dissolved once the drug is dissolved in chloroform. Aluminium foil lines the inside of a specially constructed aluminium former, and cork blocks that fit firmly are used to blank off the ends.[8]

EVALUATION PARAMETERS:

1. Interaction studies

Practically every dose form for pharmaceuticals includes experiments. The drug's compatibility with the excipients determines the stability of the formulation, among other things. It is essential to identify any potential physical or chemical interactions between the medicine and the excipients since they may impact the medication's stability and bioavailability. Only then can a stable product be produced. Compatibility studies are crucial to the development of new formulations if the excipient has never been utilised in one that contains the active ingredient. Thermal analysis, Fourier Transform Infrared spectroscopy, UV, and chromatographic techniques are frequently used in interaction studies. These studies compare the physicochemical characteristics of the materials, including assay, melting endotherms, characteristic wave numbers, absorption maxima, etc.

2. Thickness of the patch

To verify the thickness of the created patch, the thickness of the drug-loaded patch is measured at several spots using a digital micrometer. The average thickness and standard deviation for the same are then calculated.

3. Weight uniformity

Before testing, the created patches must be dried for four hours at 60^0 C. A predetermined patch area must be cut in several patch sections and weighed using a digital balance. The weight in digital balance and the average weight. From the individual weight, the average weight and standard deviation data must be computed.

4. Folding endurance

An area-specific strip is to be cut uniformly, then folded in the same spot repeatedly until it breaks. The value of folding endurance was determined by counting how many times the film could be folded in the same direction without breaking.

5. Percentage moisture content

Each weighted film piece must be weighted separately and stored in a desiccator. After containing fused calcium chloride for 24 hours at room temperature, the films need to be reweighted in order to calculate the moisture content percentage using the formula below.

Percentage moisture Content = [Initial weight - Final weight / Final weight] x 100.

6. Percentage moisture uptake

To maintain 84 percent relative humidity, the weighted films must be stored in a desiccator with a saturated potassium chloride solution for 24 hours at room temperature. The films must be reweighted after 24 hours, and the % moisture uptake must be calculated using the formula below.

Percentage moisture uptake = [Final weight-Initial weight/Initial weight] x 100

7. Water vapor permeability(WVP) evaluation

The foam dressing method can be used to measure the permeation of water vapour. The air forced oven is substituted with a natural air circulation system. One way to express the WVP is in gm/m^2 per 24 hours. A is the surface area of the exposure samples stated in m^2, and W is the amount of vapour that permeated through the patch expressed in gm/24 hours.

8. Drug content

A certain portion of the patch needs to dissolve in a given volume of an appropriate solvent. After that, the mixture must be filtered through a filter medium before the drug's content is examined using the appropriate technology (UV or HPLC). The average of three separate samples is shown by each value.

9. Thumb tack test

It is a qualitative test used to determine the adhesive's tack properties. Simply pressing the thumb against the glue allows one to identify the relative tack quality.

10. Flatness test

It is necessary to cut three longitudinal strips-one from the center, one from the left, and one from the right-from each film at three distinct portions. Each strip's length was measured, and the flatness was assessed by figuring out what proportion of constriction was equal to 100% flatness[11]

11. In vitro drug release studies

The USP apparatus V, paddle over disc method, can be utilised to evaluate the drug's release from the prepared patches. Dry films of a given thickness must be weighed, cut into a specific form, and adhered to a glass plate using an adhesive. After equilibrating the apparatus to 32 ± 0.5°C, the glass plate was submerged in 500 mL of the phosphate buffer (pH 7.4) or dissolving medium. After that, the paddle was moved to a distance of 2.5 cm from the glass plate and turned at a speed of 50 revolutions per minute. Samples (5-mL aliquots) can be taken out at predetermined intervals for up to 24 hours, and an HPLC or UV spectrophotometer can be used for analysis.Three duplicates of the experiment must be carried out so that the mean value may be determined.

12. In vitro skin permeation studies

Diffusion cells can be used to conduct an in vitro permeation research. The entire thickness of the abdomen skin was taken from male Wistar rats weighing between 200 and 250 grams. The dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, and before beginning the experiment, it was equilibrated for one hour in phosphate buffer pH 7.4 or dissolution medium. The skin was then placed on a magnetic stirrer with a small magnetic needle for uniform diffusate distribution. The abdominal region's hair should be carefully removed using an electric clip per A heater with thermostat control was used to keep the cell's temperature at 32 ± 0.5°C. With the epidermis facing upward into the donor compartment, the isolated rat skin piece is to be put between the diffusion cell's compartments. At regular intervals, a specific volume of sample must be taken out of the receptor compartment and replaced with an equivalent volume of brand-new medium. Samples must pass through the filtering media before being analysed using HPLC or spectrophotometry. Permeability coefficients were calculated by dividing the flux by the initial drug load (mg/cm^2), and flux can be directly calculated as the slope of the curve between the steady state values of the amount of drug penetrated (mg/cm^2) versus time in hours. . Permeability coefficients were calculated by dividing the flux by the initial drug load (mg/cm^2), and flux can be directly calculated as the slope of the curve between the steady state values of the amount of drug penetrated (mg/cm^2) versus time in hours.

13. Stability studies

In accordance with ICH recommendations, stability tests must be carried out by holding the TDDS sample for six months at 40+ 0.5-degree C and 75+_5% relative humidity. Samples were taken out at 0, 30, 60, 90, and 180 days, and their drug content was appropriately analyzed.[12]

ROUTES OF DRUG PENETRATION:

Diffusion through closed pathways, primarily hair follicles and the sebaceous glands they are connected to, or through the epidermis itself, are the diffusant's two possible entrance points into the blood vasculature (Barry, 1987). Consequently, there are two main penetration points.

1. Transcorneal penetration

a. Intra cellular penetration:

Drug molecules go through the stratum corneum's cells. It typically occurs when a medication is hydrophilic. Water builds up close to the protein filaments' outer surface as the stratum corneum hydrates. This immobilised water appears to be traversed by polar molecules.

b. Intercellular penetration:

Non-polar chemicals enter cells through the intercellular pathway. These molecules disperse and disintegrate in the non-aqueous lipid matrix that is incorporated between the filaments of protein.

2. Transappendegeal penetration

We refer to this as the shunt pathway. Through the hair follicles, which are the seabous channel of salty sweat glands, the medication molecules may pass through in this manner. The transappendegal route is regarded as having a small geographic area, making it of minimal significance (less than 0.1 percent of total surface). However, for big polar molecules, the pathway might be somewhat significant. The physical and chemical qualities of the penetrant—most notably, its relative capacity to partition into each akin phase—have a major influence on the rate at which permeation happens. The composite of a seris in sequence can be used to display the transdermal penetration as follows:

Adsorption of a penetrate molecules onto the surface layers of stratum corneum.

a. Diffusion through stratum corneum and thorough viable epidermis.

b. Finally, through papillary dermis into the microcirculation.

Peripheral circulation is sufficiently fast, and the viable tissue layer and capillaries are relatively permeable. Diffusion through the stratum corneum is hence the phase that limits the rate. The stratum corneum functions as a medium for passive diffusion. And now for the transdermal drug delivery system. Therefore, a straightforward multilayer model, as illustrated in fig. no.11, can be used to describe the various skin tissue layers for transdermal drug transport. [9]

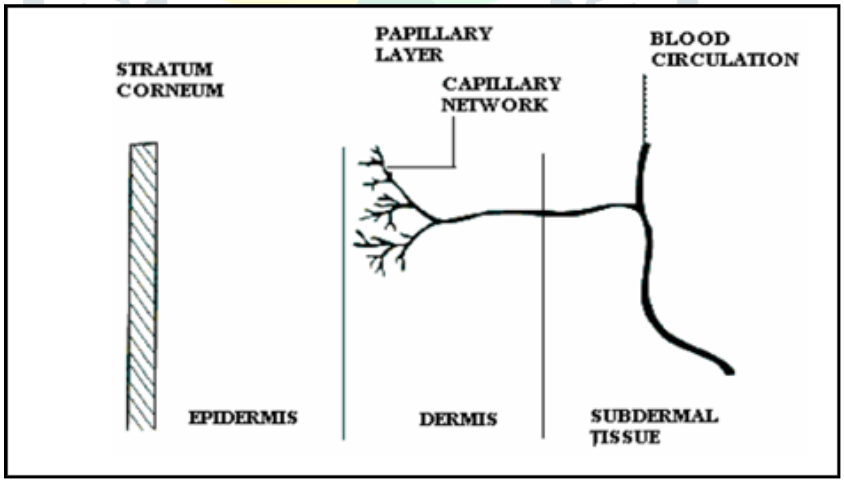

Figure no.7 mechanistic analysis of skin permeation [9]

FACTORS AFFECTING DRUG PENETRATION

Two types of factors affect the drug penetration such as biological and physiochemical factors these factors are listed below:

A. Biological factors

1. Skin age
2. Skin condition
3. Species difference
4. Blood supply

5. Skin metabolism
6. Regional skin site.

B. Physiochemical factors

(1) Temperature and pH
(2) Skin hydration
(3) Diffusion coefficient
(4) Drug content/concentration
(5) Molecular size and shape
(6) Partition coefficient.[16]

Factors influencing Transdermal Drug Delivery: The effective transdermal drug delivery can be formulated by considering three factors as Drug, Skin, and the vehicles. So the factors affecting can be divided in to classes as biological factors and physicochemical factors.

- **Biological factors**:

1. **Skin age:** Younger skin is more porous than older skin. Children are particularly vulnerable to pollutants absorbing via their skin. Therefore, one of the variables influencing medication penetration in TDDS is skin age.
2. **Skin condition:** Acids, alkalis, and a variety of solvents, including methanol and chloroform, harm skin cells and encourage penetration. Skin conditions are altered when a patient is ill. A healthy skin barrier is preferable; however penetration is impacted by the previously mentioned factors.
3. **Species differences:** The thickness, density, and keratinization of skin differ among species, which influences the penetration.
4. **Blood supply**: Changes in peripheral circulation can affect transdermal absorption.
5. **Skin metabolism:** Chemokines, hormones, steroids, and some medications are all metabolised by the skin. Therefore, the effectiveness of a medicine absorbed through the skin is determined by skin metabolism.
6. **Regional skin site:** Site-specific differences include skin thickness, stratum corneum type, and appendage density. These elements have a major impact on penetration. .[16]

- **Physicochemical factors:**

1. **Temperature and pH**: Temperature variations cause a ten-fold increase in drug penetration. With a drop in temperature, the diffusion coefficient falls. Applying solutions with extremely high or low pH values can harm the medication. Changes in pH that modify the ratio of charged to uncharged species and their transdermal permeability can impact the flux of ionizable medicines in moderate pH levels.
2. **Skin hydration:** Skin becomes much more permeable when it comes into contact with water. The most crucial element boosting skin penetration is hydration. Humectants are therefore used in transdermal delivery.
3. **Diffusion coefficient**: Drug penetration is based on the drug's diffusion coefficient. The features of the drug, the diffusion medium, and their interactions all affect the drug's diffusion coefficient at constant temperature.
4. **Drug concentration:** The gradient of concentration across the barrier determines the flow, and a higher concentration gradient indicates a higher drug concentration across the barrier.
5. **Molecular size and shape:** Molecular weight has an inverse relationship with drug absorption; smaller molecules absorb more quickly than larger ones. Partition coefficient domination obscures the impact of molecule size.
6. **Partition coefficient:** Good action requires the ideal partition coefficient (K). Medication with a high K content isn't ready to leave the skin's lipid layer. Furthermore, medications with low K won't permeate. [17]

TECHNOLOGIES FOR ENHANCING TRANSDERMAL DELIVERY

In comparison to alternative administration methods, transdermal medication delivery presents several advantages, including the ability to circumvent first pass metabolism and ease of self-administration. However, not all medications may be applied with a traditional transdermal administration technique because of the SC's hydrophobic properties and dense cellular architecture. A number of variables could influence how well a medication penetrates the skin. The physiology of the skin is the primary component that influences skin absorption. The transdermal patch's thickness and the quantity of lipid in the various skin layers where it is applied, for example, may have an impact on how quickly medications are absorbed into the skin. The amount of capillary blood capillaries in specific body areas of the skin may affect how quickly a medication enters the bloodstream. Furthermore, as a result of trans follicular drug delivery, the existence of sweat ducts and hair follicles may also help a larger amount of medicine to enter the body. Body temperature influences blood flow and skin capillary

vasodilatation, which raises absorption rates. Furthermore, by overhydrating the skin with an occlusive device, a greater degree of drug penetration may be accomplished. Since neutral keratin proteins and nonpolar lipids make up the SC, medications must be sufficiently soluble in both water and oil to be absorbed into the skin. Stated otherwise, the drug's log partition coefficient (Log P) ought to fall between 1.0 and 3.0. Traditional transdermal preparations use a drug's passive diffusion as it penetrates the skin. When a drug compound's molecular size is fewer than 600 Da, optimal medication absorption can be attained. Chemically speaking, the drug's level of ionisation greatly affects how well it absorbs through the skin. For instance, due to their hydrophobic resemblance to the SC, unionised compounds may have higher drug penetration than ionisable drugs. The drug's melting point could have an impact on how well it penetrates the skin. A medication's solubility in the SC is increased when its melting point is low, which may lead to more drug seeping into the skin. Numerous techniques have been devised by researchers to improve drug absorption via the skin, taking into account each of these aspects. An overview of the tactics used to improve transdermal medication delivery systems is shown in Figure 8. The enhancement techniques in this work are categorised by associating the kinds of ways that Barry and Morrow et al. previously described with the creation of strategies that Prausnitz and Langer categorised. Instead of using a patch system, the medicine is made into a traditional liquid spray, gel, cream, or other topical formulations in the first generation of transdermal drug delivery. These compositions are applied topically without requiring the use of complex platforms or systems. This method utilises passive diffusion to achieve absorption into the skin and so the incorporated drug must be of low molecular mass (< 600 Da), possessing sufficient hydrophobicity and must be effective in low dose administration. Some marketed transdermal products, as listed in Fig. 5, are examples of this first-generation technology, such as Duragesic® and Salonpas®.

Nevertheless, this approach has relatively limited drug delivery, which is why other more sophisticated augmentation techniques were later created. The methodologies for improving transdermal drug delivery have been divided into five categories by Barry [43] and Morrow et al. [73], as shown by the purple-shaded semi-circle in the accompanying Fig.[13]

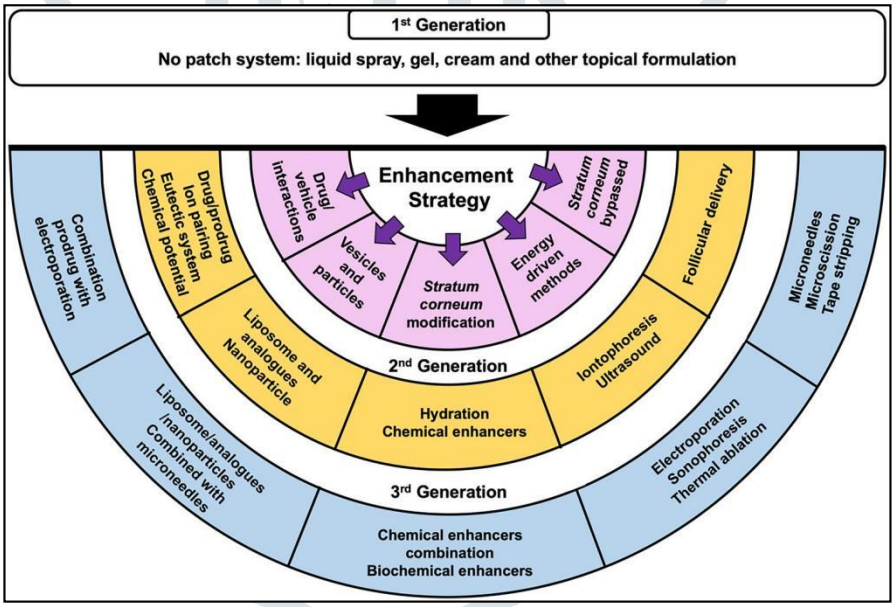

Figure no.8. Summary of the technologies utilised for enhancing transdermal drug delivery [13]

Technologies for enhancing transdermal delivery

In comparison to alternative administration methods, transdermal drug delivery presents several advantages, including the ability to bypass first pass metabolism and ease of self-administration. However, not all medications may be applied with a traditional transdermal administration technique because of the SC's hydrophobic properties and dense cellular architecture. A number of variables could influence how well a medication penetrates the skin. The physiology of the skin is the primary component that influences skin absorption. Examples of this include the transdermal patch's thickness and the quantity of lipid in various skin layer locations may affect how quickly medications are absorbed by the skin. The amount of capillary blood capillaries in specific skin areas of the body may affect how quickly drugs are absorbed into the bloodstream. There are two types of technologies that are utilised to alter the stratum corneum's barrier properties: passive/chemical technologies and active/physical technologies. To alter the stratum corneum structure, passive approaches include optimising the formulation and changing the interactions between the medication and the carrier. Chemical enhancers and emulsions, for example, are quite simple to integrate via passive ways into transdermal patches. The primary disadvantage of passive approaches, however, would be the apparent adverse effect on medications with rapid onset, such insulin, due to the lag time in drug release. [14]

Chemical penetration enhancers, which increase drug partitioning into the stratum corneum barrier domain and promote drug permeation across the skin without causing long-term skin damage, are one of the most popular passive approaches. Penetration enhancers work through a variety of ways, including: improving the drug's thermodynamic activity, the fluidity of the stratum corneum lipid bilayers, interaction with intercellular proteins, disruption or extraction of intercellular lipids, and stratum corneum hydration. There are many different kinds of penetration enhancers, and instead of categorising them according to how they work, they can be grouped according to their chemical structures. Since the majority of these have multiple modes of action, it is challenging to group them based on this attribute. Alcohols, sulphoxides, azone, pyrrolidines, essential oils, terpenes and terpenoids, fatty acids, water, and urea are a few examples of substances that are frequently studied penetration enhancers. The main drawback of penetration enhancers, however, is that there is frequently a strong correlation between their effectiveness and the incidence of skin irritation. Gels have been utilised in TDD, and new advancements in the realm of penetration enhancers have led to the introduction of new semisolid vehicle types such proniosomes and microemulsion gels. Proniosomes are non-ionic surfactant vesicles that are sometimes referred to as "dry niosomes" due to the possibility that they need to be hydrated in order for the medicine to release and permeate the skin. Because proteosomal gels function as penetration enhancers, enhancing drug permeability from the epidermal barrier, they have been utilised in TDD. Instead of using a patch system, the medicine is made into a traditional liquid spray, gel, cream, or other topical formulations in the first generation of transdermal drug delivery. These compositions are applied topically, without the need for complex platforms or systems [10]. Since passive diffusion is used in this method to promote skin absorption, the drug integrated into the skin must have a low molecular mass (<600Da), appropriate hydrophobicity, and be efficacious when administered at low doses. Nevertheless, there is relatively little medication delivery with this approach, which is why several more sophisticated augmentation methods were later created. [14]

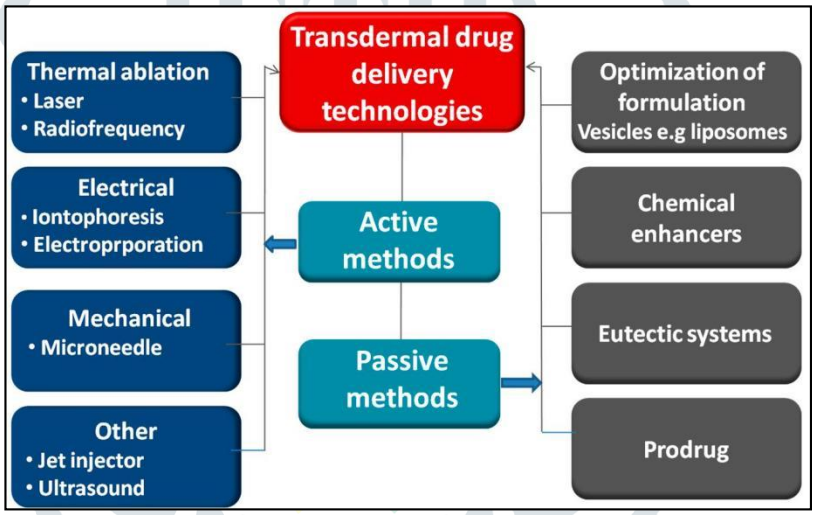

Figure.no.9 : Approaches for enhancing drug transport across the skin[14]

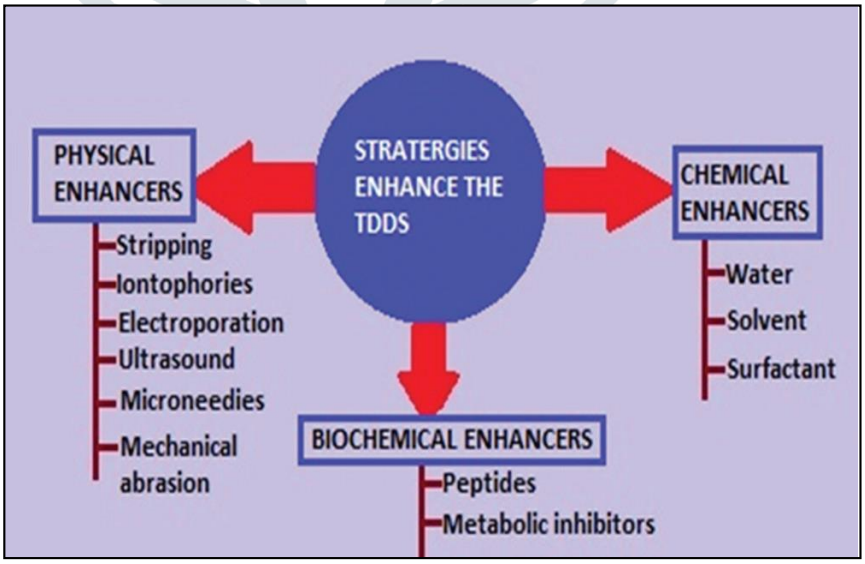

Figure no.10 : Enhancement strategies of TDDS[16]

1. There are three methods for improving TDDS (Fig. 10). They are enhancements that are chemical, physical, and biological.
2. Chemical enhancement is the process by which a molecule interacts or binds to the lipoidal membrane that makes up the stratum corneum, increasing its permeability.
3. The stratum corneum lipid membrane's permeability is directly increased by biochemical stimulation, which also indirectly influences skin permeability by altering lipid metabolism.
4. Using techniques like stripping, iontophoresis, electroporation, ultrasound, microneedles, and mechanical abrasion, physical enhancement improves medication delivery.

TRANSDERMAL MARKET

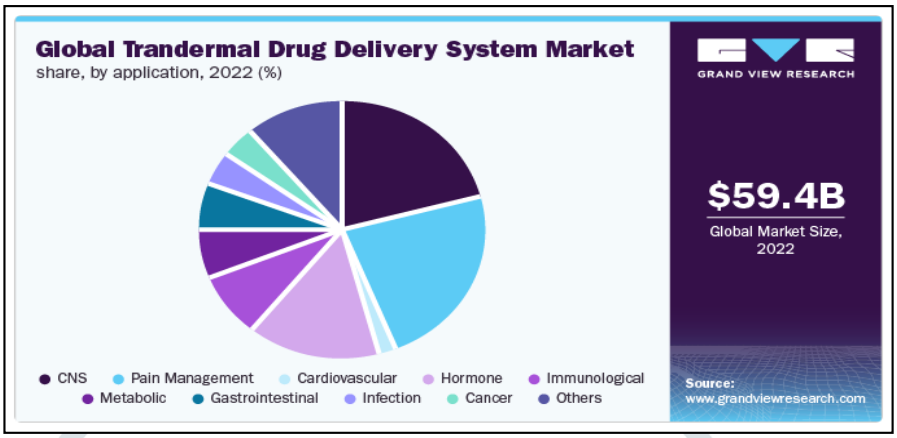

Fig no.11: global transdermal market,2022[20]

Introduction

Because the markets for transdermal drug delivery products overlap with the pharmaceutical markets for all medications administered via this route, it is challenging to characterise these markets separately. The market share of transdermal technologies in relation to all drug delivery systems can be estimated. Another way to look at the market is by calculating the share of transdermal products in different therapeutic areas although the technology used may be the same. For example, transdermal patches can be used for multiple therapeutic areas and for multiple products. In case of an individual drug delivered by a transdermal technology, it may be difficult to breakdown the total value into the two components: the drug and the delivery technology. Because they overlap with the pharmaceutical markets for all medications supplied via this route, transdermal drug delivery product markets are challenging to identify. The percentage of the drug delivery technologies market that transdermal technologies account for can be estimated. An other method of examining the market is to compute the proportion of transdermal products across various therapeutic domains, even though the underlying technology may be same. Transdermal patches, for instance, can be applied to various product formulations and therapeutic locations. When a single medication is administered using transdermal technology, it could be challenging to divide the overall worth into the substance and the delivery method. [22]

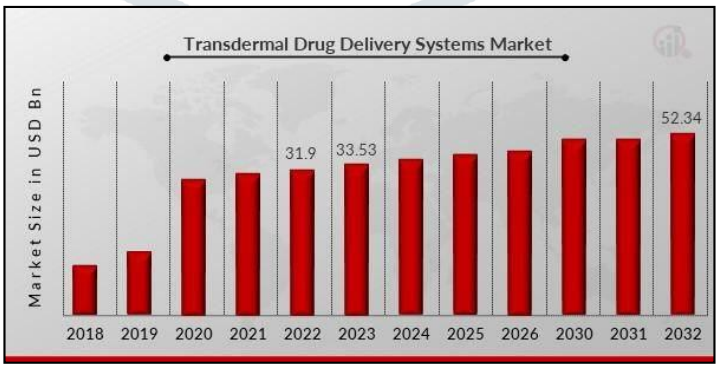

Figure No.12:Transdermal Drug Delivery Market[21]

Marketing strategies for transdermal drug delivery

Choosing an approved drug
Choosing a drug and indication where efficacy and safety can be improved by TDD
Demonstration of safety
Development of program management in relation to TDD
Performance of pharmaco-economic studies and demonstration of cost-effectiveness
To achieve cost reduction within the cost-containment restraints
To meet customer requirements and patient needs
Education of the health professionals regarding the benefits of the transdermal delivery system
Extension of life of drugs coming of patents by developing transdermal formulations
Collaboration of a drug delivery technology company with a pharmaceutical company

Table no.3: Marketing strategies based on transdermal drug delivery technologies [22]

Transdermal Drug Delivery System Market

Companies offering transdermal medication delivery systems that are currently available on the market are listed. The entire range of medications that are delivered trans dermally is manufactured using components created by 3M Pharmaceuticals, which is a leader in developing the technology components of transdermal drug delivery systems. A graph illustrating the variety of transdermal medication delivery systems now available for purchase is presented in Figure 6. The medications that are administered trans dermally are plotted on the X-axis of the graph, and the proportion of all transdermal goods that are sold in the market is plotted on the Y-axis. [23]

ADVANCED DEVELOPMENT

For passive transdermal distribution, drug in adhesive technology has emerged as the preferred method; adhesives and excipients are the subjects of two study areas in formulation. The main goals of adhesive research are to tailor the adhesive to enhance medication stability and solubility, decrease lag time, boost rate of distribution, and improve skin adherence during the use period. The transdermal formulator can maximise the effectiveness of the transdermal patch by tailoring the adhesive chemistry, as there isn't a universal adhesive that works with all medication and formulation chemistries.

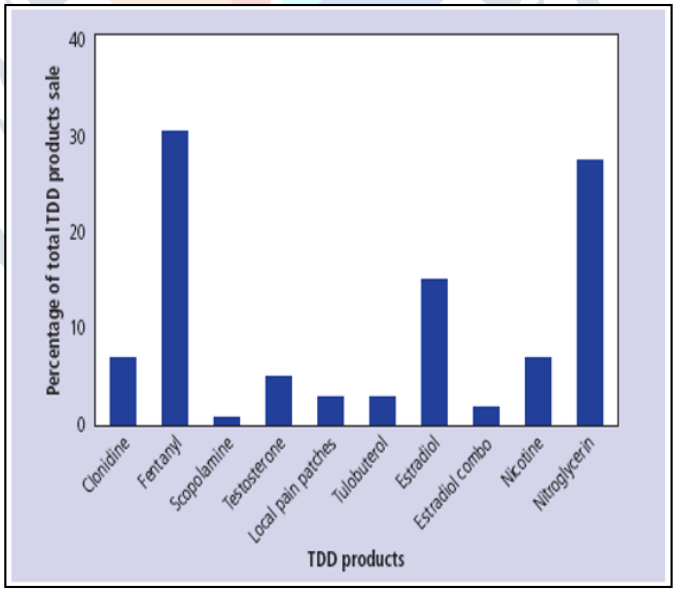

Figure no.13: Graph of Transdermal Drug Delivery Products Vs. Percentage Total Sold Transdermal Drug Delivery Products.[23]

FDA Regulation and Transdermal Drug Delivery System/Regulatory Aspects

In 1979, the FDA approved the first transdermal drug patch. Transdermal medication delivery methods have advanced significantly since then. The events in the transdermal technology sector were arranged in a chronology, with approvals received at each step of the chronology. The FDA has highly strict regulations regarding transdermal medication delivery systems. The Food and Drug Administration defines a transdermal drug delivery system as a combinational device in 21 CFR § 3.2(e). Before a transdermal patch is approved for use in the market, it must undergo premarket approval (PMA) and be supported by a considerable body of evidence, such as animal research, biomechanical testing, and clinical trial studies. The Nepro patch, which is used to treat Parkinson's disease, was recently approved as a transdermal drug delivery device. Making sure the medication is present and being administered in a stable and controlled manner is an

important issue to take into account when using a passive transdermal drug delivery system. Additionally, it's critical to comprehend how the medication reacts with skin and make sure that the materials employed to make the transdermal patch don't cause any negative side effects, including itching, inflammation, or other skin reactions. Additionally, the patch must be worn for a few hours or, in certain situations, a few days (such as a contraceptive patch). As a result, the patch's characteristics, such as the kind of polymers and adhesives employed, must be carefully considered. Polymers are utilised in the patch's construction. Polymeric polymers come in several varieties that are used to build transdermal medication delivery systems. The polymeric materials and their properties that are employed to create transdermal medication delivery systems are described in the section of the paper that follows. [23]

THE FUTURE:

Transdermal device sales are expected to reach $2 billion in the United States (Barry, 2001), accounting for 10% of the country's $28 billion medication delivery market. Considering that the FDA only approved nine more medications after the first transdermal patch was licenced in 1979, these figures are astonishing. This brief inventory of "deliverables" demonstrates the physical and chemical limitations placed on skin distribution. The inhalation market has grown at a rate of twenty percent, while oral drug delivery has grown at a rate of two percent. Transdermal drug delivery has seen a strong yearly growth rate of twenty five percent (Grosh2000). This figure will undoubtedly rise in the future as more gadgets are developed and more transdermal medications are put on the market. With the introduction of these devices, more treatments for a wider range of ailments will be administered via the skin. Subjective and objective study of these gadgets is necessary, nevertheless, to ensure that the needs of science, regulations, and consumers are satisfied. Comparing the gadgets in development to traditional transdermal patch therapy, they are more expensive and intricate. As a result, they might have mechanical and electrical parts that raise the possibility of patient safety issues as a result of subpar operation or broken equipment. Furthermore, the device's effects on the skin must be reversible because lasting harm to the stratum corneum impairs its ability to serve as a barrier and, consequently, as an organ of protection Regulatory agencies will also need proof of the device's safety when applied topically, whether for a brief or extended period of time. Therefore, in order for any of these innovative drug delivery systems to be successful and rival those that are presently available on the market, their potential market, safety, efficacy, mobility, and user-friendliness must be taken into consideration. [15]

- **Future prospects of transdermal drug delivery**

Over the next five years, the transdermal drug delivery business is expected to develop at a faster rate than the overall drug market, notwithstanding occasional regulatory slowdowns. The main segment of the transdermal delivery market at the moment is analgesic product delivery. The market for transdermal pain has grown almost entirely as a result of one very popular product, Duragesic™ (ALZA/Johnson & Johnson). A setback was the transdermal nicotine market's collapse in the US. The market for transdermal scopolamine for motion sickness is stagnant, although the following industries will develop significantly in the coming years:

- Addiction
- Alcohol abuse
- CNS indications such as cognitive problems or depression [22]

CONCLUSION:

As a helpful research resource for the research scientist working on TDDS, the Transdermal Drug Delivery System Review article provides insightful information about the transdermal drug delivery system and its evaluation process. It offers important information about the TDDS. The information above demonstrates that TDDS have a lot of potential and can be used to create promising deliverable drugs with both hydrophobic and hydrophilic active substances. More knowledge of the various biological interaction mechanisms and polymers are needed to optimise this drug delivery system. Many factors must be taken into account for transdermal medicine application to be successful. Given that the skin's primary roles are containment and protection, targeting the skin for drug administration would appear extremely challenging. For safe and efficient medication administration, a number of factors must be taken into consideration, including the patient's skin condition, the characteristics of the transdermal device, the drug's qualities, and the choice of in vivo model. One of the most innovative drug delivery systems of the future may be the transdermal method. For safe and efficient medication administration, a number of factors must be taken into consideration, including the patient's skin condition, the characteristics of the transdermal device, the drug's qualities, and the choice of in vivo model. One of the most innovative drug delivery systems of the future may be the transdermal method. Future TDDS improvements are probably going to concentrate on expanding the range of medications that are accessible for use and giving more control over therapy regimens. Particular emphasis was given to this TDDS system because of the exponential growth in interest and investment in MN technologies, as well as the many benefits that come with using this strategy.

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(21) The transdermal drug delivery systems market size was valued at USD 31.9 billion in 2022 and is projected to grow from USD 33.53 billion in 2023 to USD 52.34 billion by 2032, exhibiting a compound annual growth rate (CAGR) of 5.3% during the forecast period (2023 - 2032). The increasing prevalence of chronic diseases, where conventional drug delivery system, such as oral drugs, has lower potency due to the hepatic first-pass metabolism, is the key market driver expanding the market growth. Authoer kinjoll dey

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