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A REVIEW: TRANSDERMAL DELIVERY USING DERMALPATCHES AND MICRONEEDLES

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ABSTRACT:

Currently, approximately 74% of medications are administered orally, but their effectiveness often falls short of expectations. In response to this challenge, the transdermal drug delivery system has emerged to enhance drug delivery characteristics. Transdermal drug delivery involves the administration of drugs through the skin to achieve a systemic impact, distinct from the conventional topical approach. Transdermal drug delivery systems (TDDS) are specialized dosage forms that facilitate drug transport to viable epidermal and/or dermal tissues for local therapeutic effects, with a significant portion of the drug entering the systemic bloodstream.

The adhesive component of the transdermal drug delivery system plays a crucial role in ensuring the safety, efficacy, and quality of the product. Compared to traditional oral and invasive delivery methods, topical administration of therapeutic agents through transdermal patches offers numerous advantages. Key benefits include limiting hepatic first-pass metabolism, improving therapeutic efficiency, and maintaining a consistent plasma drug level. This article offers an overview of transdermal patches, detailing their types, preparation methods, and physicochemical evaluation techniques.

Keywords: TDDS, Topical drug delivery, Systemic blood circulation.

INTRODUCTION:

Transdermal drug delivery systems (TDDS), sometimes referred to as "patches," are dosage forms intended to distribute a medication dosage that is therapeutically efficacious through a patient's skin. To administer therapeutic drugs for systemic effects via the human skin, it is necessary to take into account the skin's complete morphological, biophysical, and physicochemical features. Transdermal administration offers a significant advantage over oral and injectable methods due to its ability to prevent first pass metabolism and increase patient compliance, respectively. In addition to enabling continuous administration of medications with brief biological half-lives, transdermal distribution also prevents pulsed entrance into systemic circulation, which frequently results in undesired side effects.

As a result, many innovative medication delivery methods, including transdermal, controlled-release, and transmucosal delivery, were developed. Transdermal drug administration has a number of significant benefits, including limiting hepatic first pass metabolism, improving therapeutic efficacy, and preserving a constant medication plasma level. The FDA approved Transdermal-SCOP, the first transdermal device, in 1979 to reduce travel-related nausea and vomiting, especially when traveling by sea. Measurable blood levels of the drug, detectable drug and metabolite excretion in the urine, and the patient's clinical response to the prescribed pharmacological therapy are all indicators of percutaneous drug absorption.

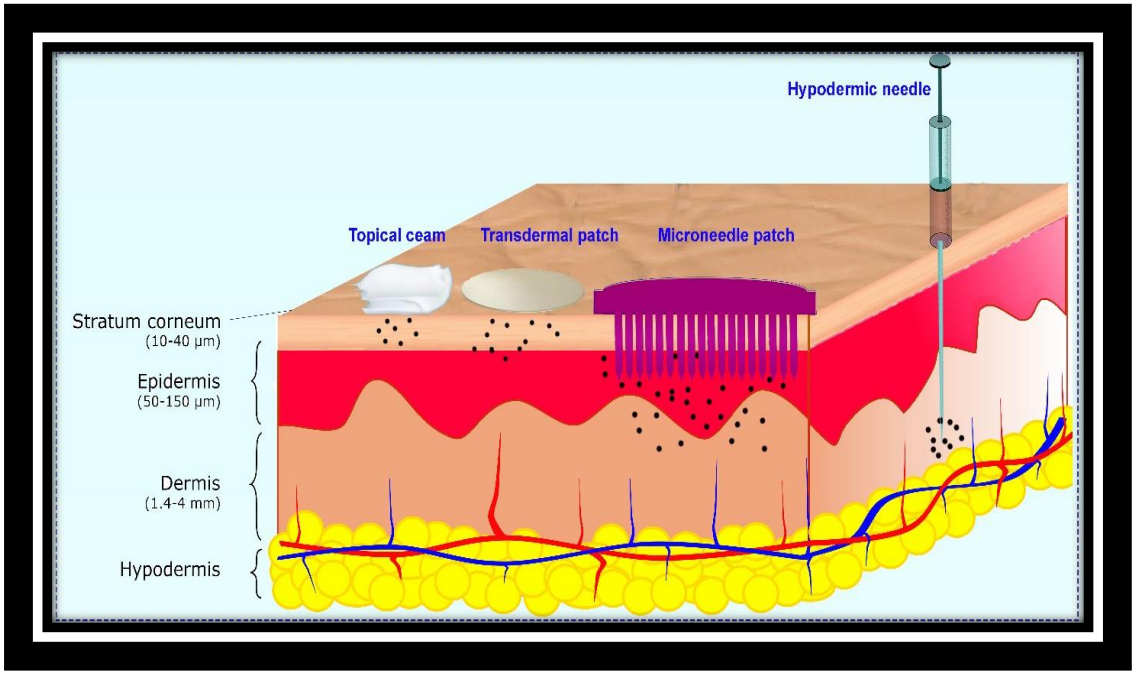

fig 1.transdermal drug delivery system

Transdermal delivery offers a compelling substitute for oral drug administration and is anticipated to offer an option to hypodermic injection as well. Since ancient times, individuals have applied drugs topically to the skin to achieve therapeutic benefits. In the present day, numerous topical formulations have been created to address specific local indications. In 1979, the US approved the use of the first transdermal method for systemic delivery, a three-day patch that treats motion sickness using scopolamine. A decade later, transdermal delivery gained more attention in medicine and from the general public when nicotine patches emerged as the first transdermal blockbuster.

When comparing transdermal delivery to the oral route, there are several advantages. It is specifically utilized in cases when the liver has a notable first-pass effect that may cause medications to be metabolized too soon. Additionally, transdermal distribution is preferable to hypodermic injections, which are uncomfortable, produce hazardous medical waste, and increase the risk of disease transmission through reused needles, particularly in underdeveloped nations. Transdermal systems can also be self-administered and are non-invasive. They have the capacity to offer relief for extended periods of time—up to a week. In addition, they enhance patient adherence, and the systems are typically affordable.[1]

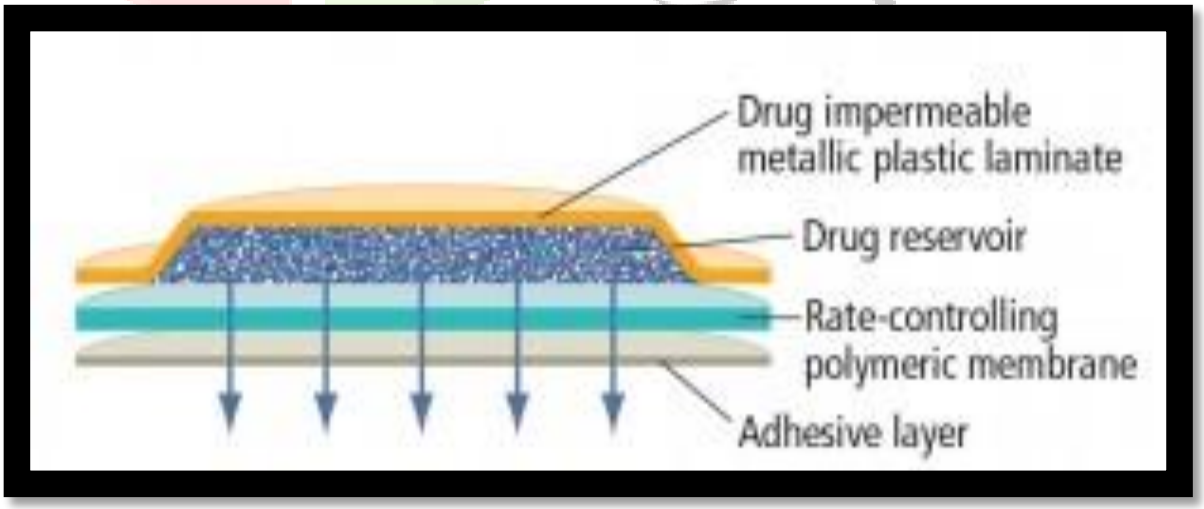

fig 2. transdermal patch

First-generation transdermal delivery system

Most transdermal patches used in clinical practice to date are products of the first generation of transdermal delivery technologies. The recent explosion in first-generation transdermal patch sales on the market has been made possible by significant advancements in patch technology and increased public acceptability. This increase will eventually level out, though, as medications with the right qualities for these kinds of systems run out. First-generation delivery candidates need to be lipophilic, have a low molecular weight, and work well at low dosages. Because of their limited oral bioavailability, the requirement or preference for less frequent dosage or consistent delivery profiles, among other reasons, transdermal delivery should typically be more appealing than oral delivery.

As an alternative to the conventional transdermal patch used in first-generation delivery systems, a metered liquid spray, gel, or other topical formulation is applied to the skin. This formulation can drive small lipophilic drugs into the stratum corneum, which acts as a drug reservoir for prolonged release of the drug into the viable epidermis over a period of hours. For instance, transdermal sprays for the delivery of estradiol have just received approval, while testosterone gels have been in use for a number of years. [2],[3]

Second generation transdermal delivery system

The next generation of transdermal administration systems understands that increasing skin permeability is necessary to increase the range of transdermal medications. The optimal enhancer should:

(i) add a driving force for transport into the skin;
(ii) increase skin permeability by reversibly altering the structure of the stratum corneum;
(iii) prevent damage to deeper, live tissues.

Nevertheless, this generation's enhancement techniques—iontophoresis, traditional chemical enhancers, and non-cavitational ultrasound—have had difficulty striking a compromise between maximizing delivery through the stratum corneum and preventing injury to deeper tissues. Consequently, distribution of macromolecules has not been much affected by this second generation of delivery technologies, which has largely improved small molecule delivery for localized, dermatological, cosmetic, and certain systemic applications.

Conventional chemical enhancers

Second-generation delivery techniques have mostly focused on the development of chemical enhancers in recognition of the necessity to increase skin permeability. Since the main focus of this method is on creating novel formulations using chemical excipients, it is a logical expansion of the conventional pharmaceutical toolset. By introducing amphiphilic molecules into the intracellular lipid bilayers in the stratum corneum to disturb the molecular packing or by extracting lipids with solvents and surfactants to produce lipid packing defects with nanometer dimensions, a variety of potent chemical enhancers can cause significant disruptions to the highly ordered bilayer structures of the intracellular lipids. Numerous chemical enhancers have been researched; these include commercially available chemicals as well as ones that were created and manufactured especially for this use, as SEPA (2-n-nonyl-1,3dioxolane) and Azon (1-dodecylazacycloheptan-2-one).

This method is hampered by the fact that enhanced skin irritation is usually correlated with higher penetration, even of tiny molecules. Delivery of small molecules has been effectively achieved using a small subset of these enhancers that increase skin permeability without causing irritation; nevertheless, their impact on the delivery of hydrophilic chemicals or macromolecules has been restricted. The application of chemical enhancers has been severely limited due to the difficulty of localizing their effects to the stratum corneum in order to prevent irritation or toxicity to living cells in the deeper skin. Overall, chemical enhancers can increase skin permeability and provide an additional driving force for transport by increasing drug partitioning into the skin (thereby increasing the concentration gradient driving diffusion).

Iontophoresis

For almost a century, the use of iontophoresis has been investigated as a means of increasing transdermal delivery. Typically, a low-voltage current is applied continuously. Iontophoresis primarily supplies an electrical driving force for movement across stratum corneum, though skin permeability may be enhanced as well. Weakly charged and uncharged substances can be moved by electroosmotic water flow, which is produced by the preferential movement of movable cations (like Na+) over fixed anions (like keratin) in the stratum corneum. Charged pharmaceuticals are transferred by electrophoresis. Iontophoresis is mostly useful for small compounds carrying a charge and some macromolecules up to a few thousand Daltons because it does not alter the skin barrier itself.

The greatest advantage of iontophoresis is its ability to scale drug delivery according to electrical current, a feature that may be easily adjusted by a microprocessor or, in certain situations, the patient. This allows complicated delivery patterns to be enabled by allowing medication distribution to be turned on, off, and even regulated over time. However, skin irritation and pain resulting from iontophoresis's general inability to localize its effects to the stratum corneum limit the maximum current and, thus, the maximum delivery rate (Prausnitz).

Non-cavitational ultrasound

When physical therapists found that utilizing ultrasonic heating probes to massage anti-inflammatory medicines into the skin boosted efficacy, ultrasound was first widely acknowledged as a skin permeation enhancer. An oscillating pressure wave that is too high for humans to hear is known as ultrasound. While some have theorized that ultrasound's pressure gradients and oscillations propel medications into the skin, it seems that the main impact is to disturb the lipid structure of the stratum corneum, increasing permeability. Non-cavitational ultrasound has often only been able to enhance tiny, lipophilic substances in relation to skin permeability. The use of more intense non-cavitational ultrasonic settings has been restricted due to the accompanying tissue heating, which can harm deeper tissue and is not directed towards the stratum corneum. Ultrasound can also be used to create cavitational bubble activity under certain circumstances; this has a variety of impacts and is covered below. [2],[3]

Third generation transdermal delivery system

Because it targets the stratum corneum, the third generation of transdermal delivery devices is expected to have a major influence on medication delivery. While maintaining protection for deeper tissues, this targeting allows for a more robust disruption of the stratum corneum barrier and, thus, more effective transdermal distribution. Thus, it has been demonstrated in human clinical trials that new chemical enhancers, electroporation, cavitational ultrasound, and more recently, microneedles, thermal ablation, and microdermabrasion (Arora, Prausnitz, and Mitragotri) can transport macromolecules, such as therapeutic proteins and vaccines, through the skin. These developments were facilitated in part by the development of technology that allow effects to be localized to the stratum corneum and the understanding that these more aggressive techniques should be considered medically appropriate due to the safety provided by localization.

Microneedles

Piercing the stratum corneum with extremely short needles is a conceptually simple approach to selectively permeabilize it. In the last ten years, microneedles have been created as a minimally invasive way to inject medications into the skin. In order to improve skin permeability to a range of tiny molecules, proteins, and nanoparticles from an extended-release patch, solid microneedles have been demonstrated to puncture the skin painlessly. As an alternative, medication formulations have been encapsulated or coated on microneedles to deliver peptides and vaccines into the skin at a regulated or quick rate. Insulin and vaccinations have been infused using hollow microneedles.

In general, microneedles

(i) increase skin permeability by creating micron-scale pathways into the skin,

(ii) can actively drive drugs into the skin either as coated or encapsulated cargo introduced during microneedle insertion or via convective flow through hollow microneedles.

(iii) target their effects to the stratum corneum, although microneedles typically pierce across the epidermis and into the superficial dermis too (Prausnitz, Gill & Park).

Notable developments in microneedle composition and design have occurred recently. Low-cost manufacturing processes have replaced the original production procedures, which included sculpting silicon-based structures in a clean environment. These techniques are now used to create microneedles using metals and polymers that are often present in parenteral formulations and FDA-approved devices. Many substances, such as tiny molecules, proteins, DNA, and virus particles, have been dip coated into microneedles (Gill & Prausnitz). Water-soluble polymers have also been used to create microneedles, encasing different substances inside the needle matrix (Lee, Park & Prausnitz). After usage, these microneedles leave no sharp medical material left since they breakdown in the skin over a few minutes. [2],[3]

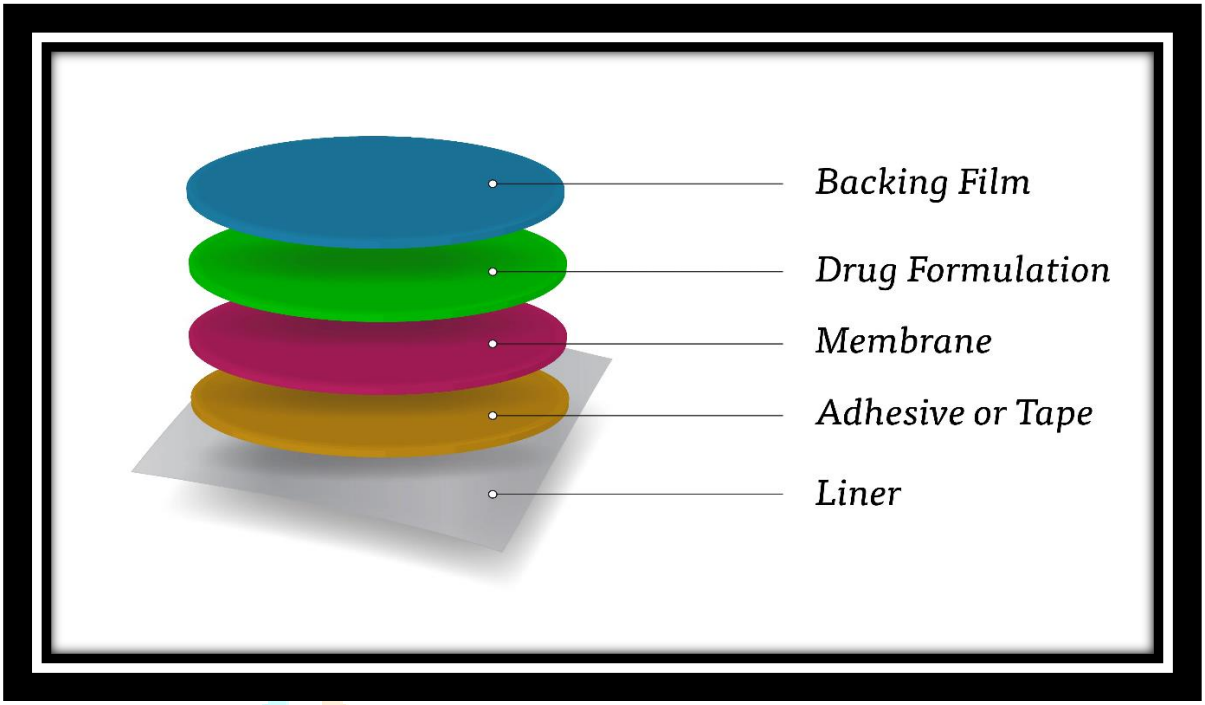

fig 3.components of a dermal patch

The common ingredients which are used for the preparation of TDDS are as follows:
Drug: Drug is in direct contact with release liner.
Ex: Nicotine, Methotrexate and Estrogen.
Liners: Protects the patch during storage.
Ex: polyester film.
Adhesive: Serves to adhere the patch to the skin for systemic delivery of drug.
Ex: Acrylates, Polyisobutylene, Silicones.
Permeation enhancers: Controls the Release of the drug.
Ex: Terpenes, Terpenoids, Pyrrolidone. Solvents like alcohol, Ethanol, Methanol. Surfactants like Sodium Lauryl sulfate, Pluronic F127, Pluronic F68.
Backing layer: Protect patch from outer environment.
Ex: Cellulose derivatives, poly vinyl alcohol, Polypropylene Silicon rubber.

TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM

a) Single layer drug in adhesive:
This sort of medication release is facilitated by the adhesive layer, which is encircled by a backing and a temporary liner. The adhesive layer not only holds the several layers together but also releases the medication onto the skin**.**

b) Multi -layer drug in adhesive:
This kind is comparable to the single layer kind as well, but in addition to the adhesive layer, it has two additional layers: one for controlled release and the other for quick medication release. The medicine is released due to the action of the sticky layer. This patch also features a permanent backing and a transient liner-layer.

c) Vapour patch:
The adhesive layer in this kind of patch has two functions: it releases vapour and holds the different layers together. Vapour patches, which are relatively new on the market, are frequently used to release essential oils to relieve congestion. There are several different kinds of vapor patches on the market that are intended to lessen the symptoms associated with cigarette smoking and enhance the quality of sleep.

d) Reservoir system:
This method embeds the drug reservoir between a rate-controlling membrane and an impermeable backing layer. Only the rate-regulating membrane—which may or may not be microporous—allows the medication to release. The medication may be in the form of a gel, suspension, solution, or disseminated across a solid polymer matrix within the drug reservoir compartment. A drug-compatible outer surface polymeric membrane made of hypoallergenic adhesive polymer can be used.

e) Matrix system:

i. Drug-in-adhesive system:

This kind uses solvent casting or melting (for hot-melt adhesives) to distribute the medicated adhesive polymer across an impermeable backing layer once the medicine has been dissolved in the adhesive polymer. Unmediated sticky polymer layers are put to the reservoir's top for protection.

ii. Matrix-dispersion system:

In this kind, the medication is uniformly distributed inside a hydrophilic or lipophilic polymer matrix. This medication-containing polymer disk is installed in a compartment made of a drug-impermeable backing layer, attached to an occlusive base plate. To create a sticky rim strip, the adhesive is not applied on the drug reservoir's face; rather, it is dispersed around its perimeter.

f) Micro reservoir system:

This kind of drug delivery system combines a matrix-dispersion mechanism with a reservoir. To create thousands of impenetrable, tiny spheres of drug reservoirs, the drug is first suspended in an aqueous solution of a water-soluble polymer and then uniformly dispersed in a lipophilic polymer. Immediately cross-linking the polymer in situ using cross-linking agents stabilizes this thermodynamically unstable dispersion. [4],[5],[6]

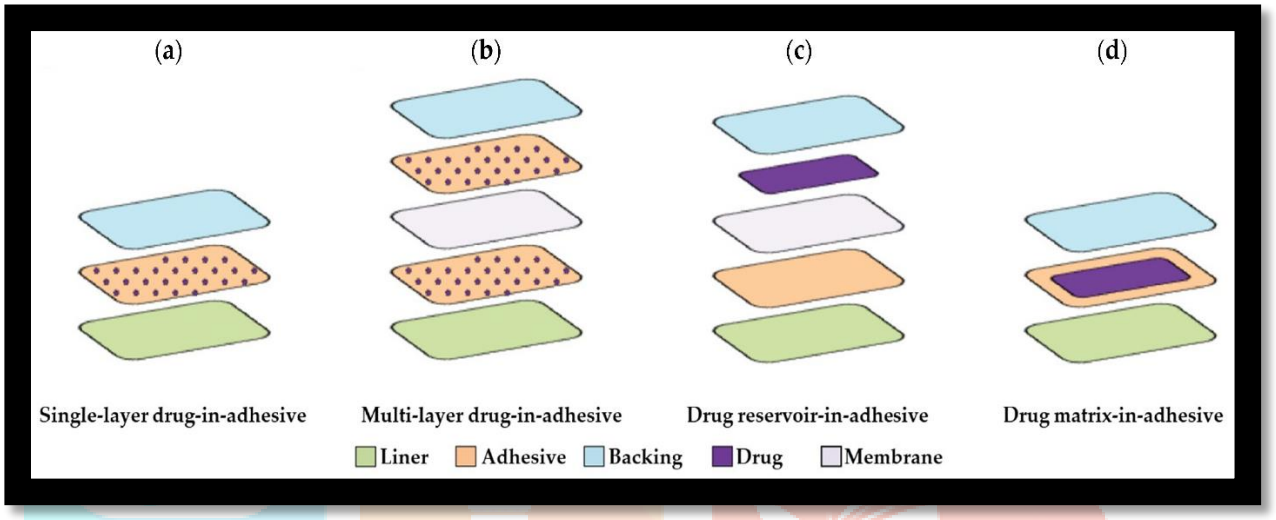

Fig 4.types of patches

MICRONEEDLE PATCH :

A sort of transdermal patch called a microneedle patch (MNPs) minimizes the drawbacks of traditional transdermal patches while maintaining their benefits. MNPs can readily pass through the stratum corneum, a 20 μm-thick layer of skin tissue that allows macromolecules up to that size. They can embed up to 102–104 needles per square centimeter of patch, and they can be coated or encapsulated with the targeted medicament.

The primary reason for the creation of MNPs is that, although macro- or large-sized molecules are difficult to distribute by selective transdermal patches, smaller or micronized molecules, such birth control and nicotine, may be readily diffused and absorbed through the skin. The needles, ranging from 100 to 1000 μm, are positioned evenly throughout the patch to ensure that patients experience minimal pain. In MNPs, two different kinds of needles are used: water-soluble needles made of soluble polymers or saccharides, and non-water-soluble needles made of metal, ceramic, or polymer.[7]

In addition to delivering molecules in other organs, MNPs may be designed for more uses than skin patches. The mouth, vagina, gastrointestinal system, and vascular wall are examples of internal surfaces that are still in development. External surfaces include the skin, eyes, fingernails, anus, and scalp. Unlike a typical transdermal patch, this enables targeting a more precise region of desired administration without depending entirely on dispersion on blood flow.

MNPs provide more effective delivery than topical or oral consumption, as was previously indicated. Researchers aim to get quicker peak concentrations (Cmax) in MNPs in drug delivery studies as compared to alternative approaches. According to the study, oral consumption takes an hour to reach peak concentration, whereas MNPs can achieve peak concentration as quickly as 20 minutes (tmax). In addition, as compared to oral consumption, the Cmax from MNPs might be up to six times greater. enabling quick delivery so that the body receives the maximum amount of the prescribed medication. This value is only equaled by direct injection; however, MNPs may be an option to achieve about the same time and concentration in cases of skin injuries and needle anxiety.[8]

Types of microneedles

There are several varieties of microneedles, each identified by their form and other attributes. Among the varieties are hollow MNPs, solid non-soluble MNPs, and soluble MNPs.

Soluble or dissolvable MNPs

Water-soluble needles composed of saccharide or soluble polymers are one kind of MNP. Dissolvable needles, however, are not an effective way to get medication to the dermal layer. The needles will disintegrate before the drug reaches the skin, therefore the maximal concentration cannot be applied there. Thankfully, scientists have created a backing layer that is insoluble in water, which prolongs the needle's useful life in the human body. Within five minutes of MNPs being applied to the skin, this design allows for the effective delivery of over 90% of the medication. [9]

Non-soluble or undissolvable MNPs

Needles constructed of metal or ceramic that won't dissolve in the body's environment are an alternative to MNPs that dissolve. Drugs may be delivered with a steady concentration using these coated needles without the needles disintegrating in the body. Although this type of MNP performs better than soluble MNPs, metal or ceramic MNPs are more traditional MNPs. The metal or ceramic MNPs may result in several waste problems, even in the case of little patches. Metal and ceramic recycling is particularly challenging since the quantities are too tiny to justify the recycling costs. For this reason, scientists are working to create dissolvable MNPs that have comparable properties to non-soluble MNPs in terms of drug delivery effectiveness. [9]

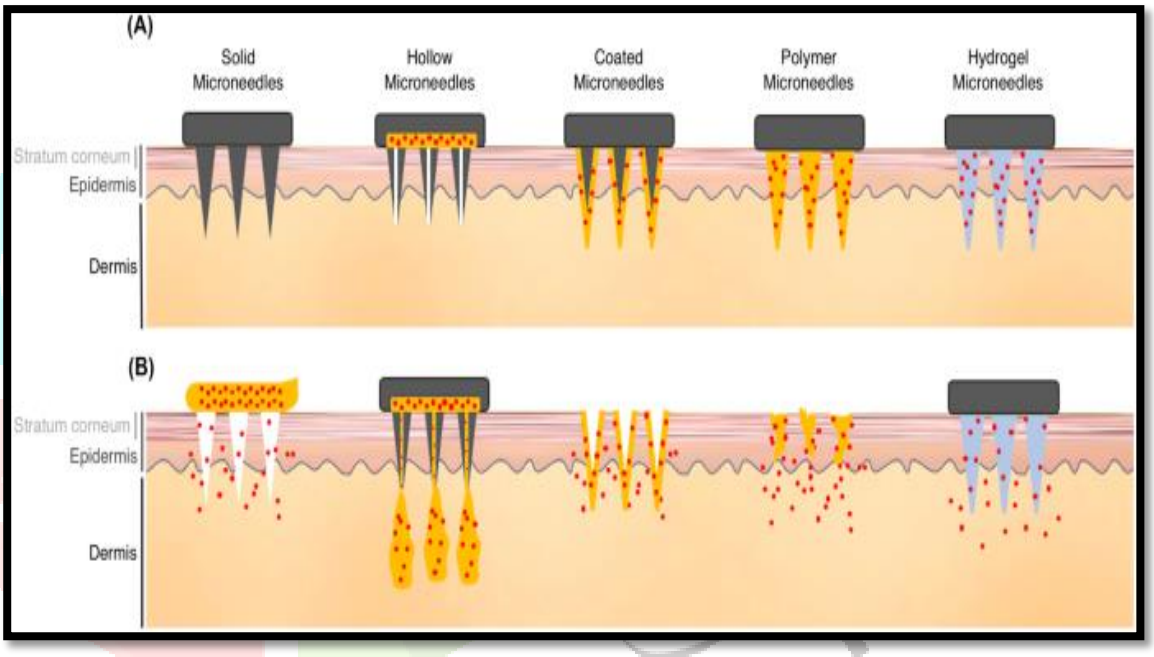

Fig 5.types of microneedle

Depending on the circumstances and the characteristics of the medicine, several MNPs may be selected.

MICRONEEDLE TYPE DEPENDING ON ACTION:

a) Solid microneedles:

Solid microneedles are the simplest form of microneedle devices and were used for most of the early work on microneedle delivery of vaccines. The solid microneedle array penetrates the tough barrier of the SC, producing channels for active molecules diffusion.

b) Hollow microneedles:

Hollow microneedles are generally made of glass, metal, silicon, ceramic and require the use of Micro-Electro-Mechanical System (MEMS).

c) Coated microneedles:

Coated MNs consists of a solid MN array (normally made of silicon or metal) coated with a drug/vaccine formulation. These MNs are applied to the skin and after insertion the coated formulation is deposited into the skin.

d) Polymer microneedles:

Dissolving microneedles are made from several bio-absorbable polymers like maltose, sugar, salmon sperm DNA (SDNA), poly (methyl vinyl ether maleic anhydride) (PMVE/MA), carboxymethyl cellulose (CMC) and polyvinylpyrrolidone (PVP)

e) Hydrogel microneedles:

Synthetic Polymer Fabricated Hydrogel-Forming Microneedles. Hydrogel MNs made from synthetic polymers can be designed to dissolve or swell in response to moisture or heat, allowing for the controlled release of drugs or other substances into the body.

Advantages:

MNPs have the potential to pierce the skin's surface, allowing drugs to enter the dermal capillaries directly and take effect quickly.

They are the ones without pain.

It has the ability to be localized to offer easy access to the targeted tissues.

Less reliant on trained medical personnel because patients themselves may safely administer MNPs.

Certain medications are poorly soluble in water; however, MNPs allows insoluble medications and chemicals to be “injected” straight into the dermal layer.

Improving the transdermal administration of insoluble medications even more.

More secure than the needle and syringe approach (needlestick). Reduced waste, no longer transmitting pathogens, and injuries. In the US, needlestick accidents cause at least 300,000 injuries a year, with disposal being a factor in about half of those cases.[11]

Application:

A vaccine against MNPs might be used in place of a direct injection. MNPs have the capacity to transport larger molecules than transdermal patches and bioactive compounds with varying physical dimensions. indicating that a pathogen or virus that is not active may be injected into the body without causing pain or rashes on the skin. It may also lower the cost of storage, as most things need to be carried in a specific condition and at a specific temperature. Co-developer of the microneedle Mark Prausnitz states on the cdc.gov website that "the ease of delivery would be a major advantage of the microneedle patch." The MNPs are small and thin compared to bottles of vial, making it possible to transport in massive quantities in a single trip. Medical waste such as syringes and dirty needles are also eliminated, reducing the possibility of pathogen transmission of blood-borne disease in rural areas.

Measles-coated MNPs may withstand greater temperatures than vial transport, according to a research. When it comes to low-income countries, where refrigeration is not a luxury, going for higher temperature resistance is a safe option. Additionally, the MNPs have control over the vaccine's distribution. less demanding the vaccination of highly qualified medical personnel in underdeveloped nations. Though it is currently in the early stages of research, the MNPs measles vaccine may lead to the creation of additional vaccines in the future. [11]

MNPs to reduce obesity

These days, one of the most talked-about issues in affluent nations is obesity. Researchers have attempted to lower the obesity prevalence by employing certain medications, such as a substance called browning chemical. MNPs are used to target specific fat tissue groups, demonstrating the patch's ability to deliver browning nanoparticles to those groups. As a result of MNPs being localized, this might lessen the adverse effects of the medication. The outcome demonstrates that over the course of four weeks, the mice's white fat shrank in the studies. Furthermore, an improved metabolism in the mice also signifies that the experiment to reduce obesity using MNPs might be worth testing in the future. If the research has been proved successful, MNPs treatment might be a great choice, as direct injection obesity drugs need medical professional assistance. While here, MNPs can be done by the patient without special skills.[12]

MNPs for cosmetic and skin care

MNPs can also include skin care products like serum for dark circles under the eyes and face lightening agents. Its localized characteristic improves the supply of skin whitening to the face. even an area as particular as dark circles under the eyes. Subjects treated with whitening agents coated in microneedles (MNPs) exhibit lower melanin index values than the whitening essence (topical) group when the melanin index (a dark or black pigment present on the skin) is measured. Eight weeks of therapy are required, and the results suggest MNPs may be a potential cosmetic vector since they can be tailored to target specific body regions and do not cause skin irritation. [12]

Safety

In addition to employing a candlestick for direct injection, another option for safety might be Micro Needle Patches (MNPs). MNPs not only encourage safer handling practices but also improved disposal and disease containment. MNPs may result in the following complications in exceptional cases.

Skin irritation

Rarely, sensitive skin individuals may experience skin irritation with MNPs. The majority of research indicates that MNPs do not cause skin irritation, but they also do not exclude the potential for those with sensitive skin.

VARIOUS METHODS FOR PREPARATION OF TDDS:

A. Asymmetric TPX membrane method:

A heat-sealable polyester film (type 1009, 3m) with a 1cm diameter concave may be utilized 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 covered with an asymmetric TPX {poly(4-methyl-1-pentene)} membrane.

The fabrication of asymmetric TPX membranes is achieved by the application of the dry/wet inversion technique. To create a polymer solution, TPX is dissolved in a combination of nonsolvent additives and a solvent (cyclohexane) at 60°C. Using a gardener's knife, the polymer solution is maintained at 40°C for 24 hours before being cast to a predetermined thickness on a glass plate. Following a 30-second evaporation of the casting film at 50°C, the glass plate must be submerged right away in a coagulation bath at a temperature maintained at 25°C. The membrane can be removed after 10 minutes of soaking and allowed to air dry for 12 hours at 50°C in a circulation oven.

B. Circular teflon mold 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 mold. To regulate solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s, the molds must be set on a flat surface and covered with an inverted funnel. For a whole day, the solvent is left to evaporate. After 24 hours, the dried films must be kept at

C. Mercury substrate method:

This approach dissolves the medication in a polymer solution with the plasticizer. To create a uniform dispersion, the aforementioned solution should be mixed for ten to fifteen minutes. Then, it should be poured over a flat mercury surface and covered with an inverted funnel to prevent solvent evaporation.

D. 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 it is then swirled for 12 hours. Triethanolamine is to be added to the dispersion in order to neutralize 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.

E. By using "EVAC membranes" method:

Polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes, and 1% Carbopol reservoir gel can all be utilized as rate control membranes to set up the goal transdermal treatment system. Gel is made using 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 neutralized using a 5% w/w sodium hydroxide solution. The medication (in gel form) is applied to a backing layer sheet that covers the designated region. To create a leak-proof device, a rate-regulating membrane will be put over the gel and the edges will be heated to seal.

F. 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 sticky film approach with aluminum 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 medication is dissolved in chloroform. Aluminum foil is used to line a specially constructed aluminum former, and cork blocks that fit firmly are used to blank off the ends.

G. Preparation of TDDS by using proliposomes:

The film deposition technique is used in the carrier approach to create the proliposomes. An optimal dosage of lecithin in a ratio of 0.1:2.0 can be obtained from the previous reference medication. To create the proliposomes, 5 mg of mannitol powder is added to a 100 ml round-bottom flask that is kept at a temperature between 60 and 70 degrees Celsius. The flask is then swirled at a speed of 80 to 90 rpm while the mannitol is dried under vacuum for 30 minutes. The water bath's temperature is brought down to 20–30°C after drying. A 0.5 ml aliquot of the organic solution is added to the round-bottomed flask at 37°C after the drug and lecithin have been dissolved in an appropriate organic solvent mixture. After the solution has completely dried, another 0.5 ml aliquot of the solution is to be added. Following the final loading, the proliposome-containing flask is attached in a lyophilizes manner. The drug-loaded mannitol powders (proliposomes) are then left in a desiccator for the whole night before being sieved through a 100 mesh screen. Until it is characterized, the gathered powder is kept at the freezing temperature in a glass bottle.

H. By using free film method:

Casting on a mercury surface creates a free film of cellulose acetate. Chloroform is to be used to make a 2% w/w polymer solution. Plasticizers must be added at a 40% weight-to-weight ratio of the polymer. A glass ring set over the mercury surface in a glass petri dish was filled with five milliliters of the polymer solution. An inverted funnel placed above the petri dish regulates the solvent's rate of evaporation. After the solvent has completely evaporated, the mercury surface is examined to detect the creation of a layer. Before being used, the dried film will be removed and kept in a desiccator in between the wax paper sheets. The volume of the polymer solution may be adjusted to create free films with varying thicknesses. [4],[5],[6]

EVALUATION PARAMETERS:

1. Interaction studies:

Excipients are essential parts of practically every dose form used in medicine. The drug's compatibility with the excipients determines the stability of a 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 creation of novel formulations if the excipients have never been utilized in formulations with the active ingredient. Thermal analysis, FT-IR, UV, and chromatographic techniques are frequently used in interaction investigations. These techniques compare the physicochemical characteristics of the materials, including assay, melting endotherms, distinctive wave numbers, absorption maxima, etc.

2. Thickness of the patch:

To guarantee the thickness of the prepared patch, the thickness of the drug-loaded patch is measured at various spots using a digital micrometer, which also calculates the average thickness and standard deviation for the same.

3. Weight uniformity:

Before testing, the prepared patches must dry for four hours at 60°C. A predetermined patch area needs to be divided into several sections, then weighed using a digital balance. The individual weights must be used to get the average weight and standard deviation values.

4. Folding endurance:

It is necessary to cut a strip of a certain area uniformly and fold it at 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:

The produced films must be weighed separately and stored for 24 hours at room temperature in a desiccator filled with fused calcium chloride. The films must be reweighed after 24 hours, and the % moisture content may be calculated using the formula below. Moisture content percentage is calculated as [original weight - final weight / final weight] times 100.

6. Percentage moisture uptake:

To maintain 84% 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 reweighed after 24 hours in order to calculate the percentage of moisture absorption using the formula below.

[Final weight- starting weight/ starting weight] × 100 is the percentage of moisture absorbed.

7. Water vapour permeability (WVP) evaluation:

Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula:

$$WVP=W/A$$

Where, WVP is expressed in gm/m^2 per 24hrs,

W is the amount of vapour permeated through the patch expressed in gm/24hrs and

A is the surface area of the exposure samples expressed in m^2

8. Drug content:

A predetermined patch area has to dissolve in a predetermined volume of an appropriate solvent. After that, the mixture must be filtered through a filter media 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. Uniformity of dosage unit test:

To fully extract the medicine from the patch, chop up a precisely weighed amount of the patch, move it to a volumetric flask of a certain capacity, dissolve it in an appropriate solvent, sonicate the mixture, and add more medication as needed. After letting the resultant solution settle for about an hour, the supernatant was appropriately diluted with the right kind of solvent to achieve the required concentration. A 0.2m membrane

filter was used to filter the solution, and it was then subjected to an appropriate analytical technique (UV or HPLC) to determine the drug concentration of each piece.

10. Polariscope examination:

This test will be carried out using a polariscope to look at the drug crystals from the patch. To determine if the drug is present in the patch in an amorphous or crystalline form, a certain surface area of the piece must be retained on the object slide and examined for drug crystals.

11. Shear adhesion test:

The purpose of this test is to determine an adhesive polymer's cohesive strength. The molecular weight, degree of crosslinking, 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 make the tape 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. The shear strength increases with the length of time required for removal.

12. Peel adhesion test:

Peel adhesion is the term used in this test to describe the force needed to remove an adhesive covering from a test substrate. The variables that affected the peel adhesion qualities were the adhesive polymer's molecular weight and the kind and quantity of additives. A single tape is put to a backing membrane of choice or a stainless steel plate. The tape is then pulled away from the substrate at a 180-degree angle, and the force needed to remove the tape is measured.

13. Thumb tack test:

It is a qualitative test used to determine the adhesive's tack properties. All that is needed to determine the relative tack quality of the glue is pressing the thumb down on it.

14. Flatness test:

Each film has to have three longitudinal strips cut out of it, one from the center, one from the left, and one from the right. Each strip's length was measured, and the percentage of constriction—0% constriction being equal to 100% flatness—was used to calculate the length variation resulting from non-uniformity in flatness.

15. Percentage elongation break test:

The length immediately preceding the break point should be noted in order to calculate the percentage elongation break. This may be done using the method below.

Elongation percentage = L1-L2/L2×100

Where, L1is the final length of each strip and L2 is the initial length of each strip.

16. Rolling ball tack test:

This test quantifies a polymer's talk-related softness. A 7/16-inch-diameter stainless steel ball is thrown into an inclined track in this test, causing it to roll down and come into touch with an adhesive that faces upward and horizontally. The tack measurement, measured in inches, is derived from the distance the ball travels along the adhesive.

17. Quick stick (peel-tack) test: In this test, the tape is pulled at a pace of 12 inches per minute and 90ºC away from the substrate. Tack value, measured and documented in ounces or grams per inch width, is the peel force needed to break the binding between adhesive and substrate.

18. Probe tack test:

This test involves touching the adhesive with the tip of a clean probe that has a predetermined surface roughness to see if a bond forms between the probe and the glue. It breaks mechanically when the probe is removed later. Tack is the unit of measurement for the force needed to remove the probe from the adhesive at a set pace. It is represented in grams.

19. In vitro drug release studies:

The drug release from the produced patches may be evaluated using the paddle over disc method (USP equipment V). Dry films of a given thickness need to 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 media. Next, the paddle was moved at a pace of 50 revolutions per minute and positioned 2.5 centimeters apart from the glass plate. Samples (5-mL aliquots) can be taken out at predetermined intervals for up to 24 hours, and UV spectrophotometer or HPLC analysis can be performed. Three duplicates of the experiment must be carried out so that the mean value may be determined.

20. In vitro skin permeation studies:

A diffusion cell can be used to conduct an in vitro permeation research. Completely developed abdomen skin in male Wistar rats weighing 200–250 grams. The dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels before starting the experiment. It was then equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 and placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The abdominal region's hair should be carefully

removed using an electric clipper. The thermostatically regulated heater was utilized to keep the temperature of the cell at 32 ± 0.5°C. With the epidermis pointing upward into the donor compartment, the isolated rat skin piece is to be put between the diffusion cell's compartments. At regular intervals, a certain volume of sample must be taken out of the receptor compartment and replaced with an equivalent volume of fresh medium. Samples must pass through a filtering media before being subjected to HPLC or spectrophotometric analysis. The permeability coefficients were derived by dividing the flux by the initial drug load (mg cm2) and flux may be directly computed as the slope of the curve between the steady-state values of the quantity of drug penetrated (mg cm-) vs. time in hours.

21. Skin irritation study:

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) has 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 damage being divided into 5 classes.

22. Stability studies:

In accordance with the ICH standards, stability tests must be carried out by keeping the TDDS samples for six months at 40±0.5°C and 75±5% relative humidity. The samples were taken out at 0,30,60,90, and 180 days, and their drug content was appropriately analyzed. [4],[5],[6]

CONCLUSION: -

For the benefit of research scientists working on transdermal drug delivery systems, this article offers useful insights on these transdermal drug delivery systems as well as an overview of the review procedure. The information above article the immense promise of TDDS, since it may be used to create promising deliverable medications with both hydrophobic and hydrophilic active substances. More knowledge of the various biological interaction processes and polymers are needed to optimize this drug delivery method. A feasible real-world use for TDDS is the upcoming generation of medication delivery systems.

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