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Transdermal Drug Delivery System: The Challenges, Advanced Drug Carriers Approaches

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Abstract: A Transdermal Drug Delivery System (TDDS) is a pharmaceutical formulation designed to deliver a specific dose of medication through the skin and into the bloodstream over a prolonged period of time. It involves applying a medicated patch or formulation to the skin surface, where the drug is absorbed through the skin layers and enters the bloodstream. This method offers advantages like avoiding the gastrointestinal tract, improving patient compliance, and providing controlled and sustained drug release. The Transdermal Drug Delivery System (TDDS) plays a significant role in modern drug administration due to its numerous advantages. One of the key benefits is improved patient compliance, as it offers a painless, non-invasive method of drug delivery that is simple and convenient to use. TDDS provides controlled and sustained release of medication, ensuring consistent drug levels in the bloodstream and reducing the frequency of dosing. To overcome the challenges, advanced drug carriers such as microspheres, microcapsule, liposomes, niosomes, nanogel and various nanoparticles have been developed. These carriers enhance drug penetration, protect active ingredients from degradation, and offer controlled and targeted drug release. TDDS play an vital role in the future of personalized medicine and advanced healthcare solutions. Therefore trans dermal drug delivery system is the fastest growing technology in the pharmaceutical industries.

Index Terms - microspheres, microcapsule, liposomes, niosomes, nanogel

I. INTRODUCTION

Many medications are now taken orally, however they aren't always as effective as they should be. To improve this, TDDS was developed. Delivery of drugs A transdermal drug delivery system is one that delivers the medication through the skin and achieves a systemic impact [1].A group of physicochemical technologies that may regulate the release and transport of pharmacologically active chemicals into cells, tissues, and organs such that these ac tivesubstances can have the best possible effects are collectively referred to as drug delivery systems (DDS)[2,3].To put it another way, DDS addresses the drug formulations and modes of administration that effectively deliver the medication to optimize therapeutic efficacy and minimize adverse effectss[3,4].TDDS, as opposed to traditional direct administration routes that involve needle-based injections, has emerged as one of the most popular non-invasive drug delivery methods through the skin. The distribution of many therapeutic substances has been greatly impacted by TDDS, particularly in the areas of pain management, hormone therapy, and the treatment of illnesses affecting the central nervous system and cardiovascular system[5,6,7,8].Transdermal patches, often known as skin patches, are medicinal adhesions that little between and within patients. The primary goal of a transdermal drug delivery system is to distribute medications through the skin at a predefined rate with little fluctuation between and within patients [9,10].

A transdermal patch is a specialized medicated patch made to distribute medications into the bloodstream via the skin's layers at a regulated pace. Since these patches are painless and can deliver continuous treatment for several days, they present a very practical way to administer medications. They are also readily discontinuable at any time. Transdermal patches can have more than one active component and are available in different sizes. These patches employ diffusion techniques to transfer these active chemicals straight into the bloodstream when they are placed to the skin. High concentrations of the active ingredient may be present in some patches, which stay on the skin for a long time. An important turning point in this drug delivery technique was reached in 1985 when the first transdermal patch containing nitroglycerin was created. Patches with a rate-controlling ethylene vinyl acetate membrane were created by Gale and Berggren. Many medications, including scopolamine (hyoscine), nicotine, estradiol, fentanyl, clonidine, and estradiol with norethisterone acetate, are prepared as transdermal patches. The type of medication therapy determines the precise location for patch application[11].

ADVANTAGES OF TDDS

1. Transdermal administration guarantees a prolonged and continuous penetration of a material over an extended period of time, preventing first-pass metabolism. [12]
2. By using transdermal medication delivery, gastrointestinal absorption and the problems of enzymatic and pH-related deactivation can be avoided.
3. In comparison to alternative dosage forms that necessitate more frequent dose administration, they provide prolonged therapy with a single application, enhancing compliance. Day 4 of transdermal clonidine.
4. Reducing unwanted side effects.
5. The cost of transdermal patches is low. [13,14]
6. Transdermal delivery is emerging as one of the most widely recognized drug delivery techniques because of ongoing innovation advancements and the ability to deliver the medication to the site of action without causing skin disruption.[15]

Because it improves the blood concentration-time profile and stops drugs from entering the bloodstream by pulse entry, it boosts therapeutic efficacy and reduces side effects.

7. It uses the drug reservoir and regulated release properties of the therapeutic delivery system to extend the activity of drugs with short plasma half-lives.
8. When oral delivery is inappropriate—for example, when vomiting or diarrhea occurs—it takes its place.
9. It guarantees long-term, steady performance and the ability to replicate zero order dynamics.[16]

DISADVANTAGE OF TDDS

1. Medication that requires high blood levels cannot be given; only strong compounds, 10 mg or less per day, are allowed.
2. The medication should have a reasonable molecular size so that it may be absorbed via the skin.
3. The drug's difficulty passing through human skin and the skin's barrier function.[17]
4. No use of ionic drugs
5. May cause allergic reaction
6. Transdemal therapy is suitable for certain drugs only.[18]

LIMITATIONS OF TRANSDERMAL DRUG DELIVERY SYSTEMS [19]

1. Some of the limitations of TDDS can be addressed with innovative techniques, including electroporation, ultrasonography, and iontophoresis.
2. The skin permeability of transdermal medication delivery systems is restricted
3. It is limited to strong medications and long lag times
4. The presence of skin enzymes, such as peptidases, prior to systemic metabolism may metabolize drugs into inactive forms and decrease their potency.
5. Given that solute diffusivity is inversely correlated with molecular weight and that big molecules cannot be used, a molecular weight of less than 500 Dalton is necessary to guarantee easy diffusion over the SC.

ANATOMY AND PHYSIOLOGY OF SKIN

The skin, the biggest organ in the human body, is about two square meters in size and receives almost one-third of the blood flow[20].The skin is categorized into the three primary layers, the outer layer is known as epidermis. The middle layer is dermis and innermost layer is referred as hypodermis

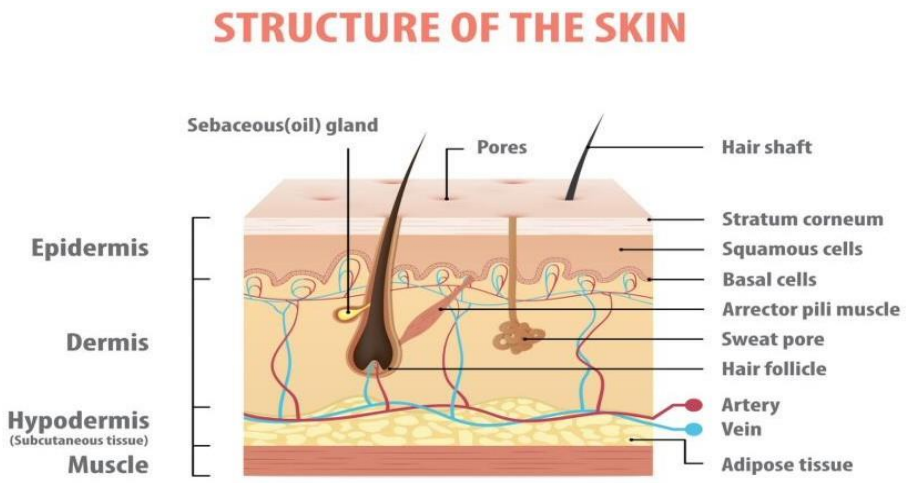

Fig 1 structure of skin

EPIDERMIS

The skin the outermost layer of the skin is called the epidermis. It has no blood vessels and offers a watertight barrier. Keratinocytes, which manufacture the protein keratin and contribute to the toughness and protection of the skin, are cells that make up the epidermis. Melanocytes, which give skin its color, and Langerhans cells, which are essential immune system components, are found in the epidermis.

The epidermis has several sub- layers, including:

1. Stratum corneum
2. Stratum granulosum
3. Stratum spinosum
4. Stratum basale

Layers of skin cells make up the epidermis. Keratinocytes comprise the majority of these cells. They comprise around 95% of the epidermis' cells. Merkel cells, Langerhans cells, and melanocytes are among the several cell types found in the epidermis[21]. It is the skin's thin, hard outermost layer. The cells that make up the epidermis are primarily Keratinocytes are cells that make up the basal layer, the innermost layer of skin. The outermost layer of the epidermis is made up of dead cells that form a barrier-like structure. This layer serves as a barrier; while many medications cannot pass past it, lipotropic medications can more readily do so than hydrophilic ones [22]. The stratum corneum Is an extremely thin layer that sits on top of the epidermis. It affects everything around us and is found on the very surface of our skin. This layer is unique since it protects our bodies. Its water content and thickness are crucial. Tough proteins (70 percent keratin) and a small amount of fat (20 percent lipid) make up the stratum corneum. [23]

DERMIS

The dermis, which is thicker than the epidermis and measures 3 to 5 mm, is situated beneath it.The dermis houses the skin's appendages and sensory receptors and is in charge of supplying nourishment to the epidermis. It comprises diverse structures, such as:

1. Blood vessels
2. Hair follicles
3. Sweatglands 4.Sebaceous glands
5. Nerve endings
6. Collagen and elastin fibers [24]

The cutaneous blood supply is essential for controlling body temperature, supplying the skin with nutrients and oxygen, and getting rid of waste and pollutants. The majority of molecules can pass through the skin

barrier more easily since capillaries are located within 0.2 mm of the skin's surface. As a result, the blood supply keeps the cutaneous concentration of a permeate extremely low[25].

HYPODERMIS

The hypodermis, or subcutaneous tissue, is the deepest layer of the skin and is made up of connective tissue and adipocytes, or fat cells. This layer acts as a cushion to protect the body's bones and organs from shocks and as an insulator to assist control body temperature. In order to enter our bloodstream, medications that are given topically, such as creams or patches, must pass through these three layers. Certain medications must penetrate much further, entering the bloodstream. However, for the majority of skin treatments to be successful, they only need to penetrate the stratum corneum, the outermost layer, and remain within the skin layers[26]. The hypodermis, sometimes referred to as subcutaneous fat tissue, is essential for maintaining the dermis and epidermis. It stores fat, aids in controlling body temperature, provides nutritional support, and offers mechanical protection[27].

FUNCTION OF SKIN [28]

1. Offers a barrier of defense against harmful substances and physical, mechanical, and thermal harm.
2. Helps to keep skin hydrated by preventing moisture loss.
3. Lessens the negative effects of the sun's UV radiation.
4. Serves as a sensory organ that enables humans to perceive temperature changes and touch.
5. Helps control body temperature by allowing perspiration and cooling the body as needed.
6. Serves as an immunological organ that may identify and treat illnesses.
7. Contributes to the synthesis of vitamin D upon exposure to sunshine.

NOVEL DRUG CARRIER

Novel Drug Delivery Systems (NDDS) are designed to deliver a certain quantity of medication to a specific location within the body while maintaining the drug's concentration and delivering the medication to the targeted tissue in a regulated fashion. The different carrier-based NDDS products include:

1. Nanoparticles
2. Microspheres
3. microcapsule
4. Drug-Carrying Resealed Erythrocytes
5. Niosomes
6. Liposomes
7. Nanogel

1. **Nanoparticles**

SLNs are colloidal nanoparticles composed of solid lipids at room temperature that range in size from 10 to 1000 nm. Structure: The solid lipid core of these nanoparticles (such as triglycerides and glycerol monostearate) is held in place by surfactants (such as lecithin and polysorbates) to enhance dispersibilty aggregation in aqueous media.

Applications: To improve medication stability, bioavailability, and prolonged release characteristics, SLNs are employed in drug delivery. Additionally, they are used in the food industry to encapsulate flavors and nutraceuticals and in cosmetics to release active substances under controlled conditions.

Benefits include: regulated release kinetics, preservation of encapsulated medications from enzymatic degradation, and a high drug loading capacity brought on by the crystalline structure of lipids.

Limited in scaling up, difficulties encapsulating hydrophilic medicines and lipid polymorphism causing drug expulsion during storage are some potential drawbacks.[29]

2. **Liposomes**

Liposomes are tiny, spherical structures composed of an aqueous (water-based) core surrounded by one or more lipid layers. Usually made up of phospholipids like phosphatidylcholine, these lipid layers can also occasionally contain cholesterol to improve their firmness and durability.

Structure: A protective barrier is created by the amphiphilic lipid bilayers found in liposomes, which have hydrophilic (loving water) heads pointed outward toward theaqueous environment and hydrophobic (repelling water) tails pointed inside. Because of their unique structure, liposomes can effectively transport a variety of medications by encasing hydrophilic drugs in their aqueous core and hydrophobic chemicals in their lipid bilayers.

Application: Because liposomes can improve a drug's solubility, stability, and bioavailability, they are essential for drug administration. They are very versatile for therapeutic applications since they may encapsulate a wide range of compounds, including tiny molecules, peptides, and nucleic acids. In addition to medicine, liposomes are used in diagnostics for imaging agents and in cosmetics to deliver active components. Their significance in contemporary biological and pharmaceutical domains is highlighted by their adaptability and efficacy in a range of applications.

Benefits: Liposomes are biocompatible and biodegradable can prolong the duration that pharmaceuticals circulate in the bloodstream, protect encapsulated medications from degradation, and target particular tissues or cells by altering their surfaces (e.g., PEGylation).

Cons: Difficulties include the possibility of instability during storage (which could cause leakage or aggregation), variations in size distribution, and possible immune system recognition and clearance [30]

3. **Niosome**

Niosomes are liposome-like vesicular systems made of cholesterol or other stabilizers and non- ionic surfactants like the Span and Tween family.

Structure: Noisomes self-assemble non-ionic surfactants in aqueous conditions to form closed bilayer structures, just like liposomes do. The membrane is further strengthened by the addition of cholesterol or other stabilizers, which increases its rigidity and stability.

Applications: To increase drug bioavailability and lower toxicity, niosomes are typically employed in drug delivery. They work particularly well for administering hydrophobic medications, vaccinations, and active ingredients in cosmetic products. Applications for niosomes in agriculture and gene delivery are also being investigated.

Benefits: Niosomes have a number of benefits over liposomes, such as increased stability, the capacity to encapsulate medications that are hydrophilic or hydrophobic, and adaptability in changing the surface properties and membrane composition. Disadvantages: However, niosomes face challenges such as limited drug loading capacity compared to liposomes, potential toxicity associated with surfactants used in their formulation, and difficulties in achieving uniformity in vesicle size and shapes [31]

4. **Microspheres**

Microspheres are free-flowing, biodegradable, solid, spherical particles that range in size from 1 to 1000 µm and are made of proteins or synthetic polymers[32]. Microspheres are made to improve the drug's therapeutic efficacy and bioavailability, which reduces toxicity and minimizes adverse effects.[33]

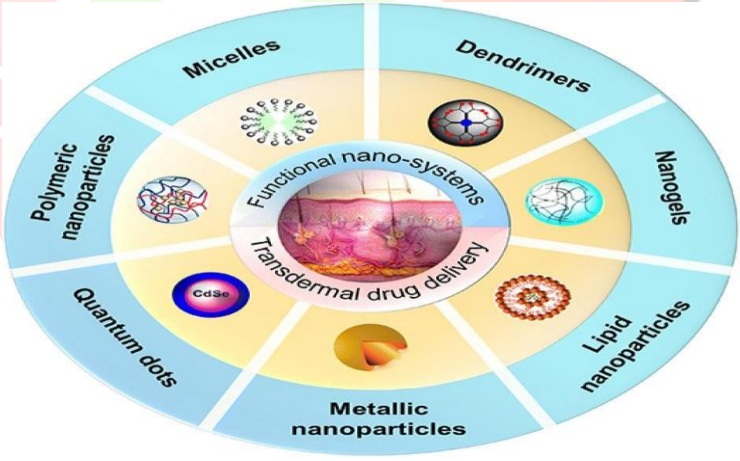

Fig 2 Novel carriers of TDDS

ADVANCEMENT IN TRANSDERMAL DRUG DELIVERY SYSTEM

1) **Electroporation**

An electrical pulse with a DC voltage greater than 100 volts [milliseconds] is applied in this manner. The lipid bilayer of the coenocyte's, the outermost cells of the epidermis, may develop transient pores or apertures as a result of this electrical pulse. By allowing molecules that could not otherwise pass through the epidermis to pass through, electroporation improves transdermal medication delivery. It works very well on tiny charged molecules. Better medication delivery is possible when high voltage is applied because it can cause

aqueous pores to develop in the epidermis[34].In bulk electroporation, the pulse strength typically controls the permeabilization's coverage area, whereas the pulse duration is more closely linked to the total pore size.[35]
Benefits: By modifying the electroporation parameters, the pace and extent of transdermal penetration can be regulated[36]. Comparatively painless and safe technique that has been proven to effectively give LMW medication. [37]

2) **Sonophoreis**

Sonophoreis is the term for the method you are describing, which uses ultrasonic waves with an energy range of usually 20 kHz to 16 kHz to move drug molecules during transdermal drug administration. By raising the skin's temperature, sonophoresis breaks down the skin's protective layer and permits medication molecules to enter the skin's various layers. The medicine is frequently combined with a particular coupling agent, like a gel or cream, to speed up this process. The heat effect produced by ultrasound waves, which facilitates drug molecule penetration, is the basic idea underlying sonophoresis.These ultrasonic waves have a 4-6 cm depth of penetration into the skin. In addition to transdermal drug delivery, sonophoresis is utilized to treat ailments like bursitis, tendinitis, and muscle soreness [38]. Furthermore, as you indicated in your earlier mail, iontophoresis is the process of transporting ionic or nonionic medicines in vivo by applying an electrochemical potential gradient. Both methods provide useful choices for improving medication distribution through the skin[39].

Lithotripsy, liposuction, cataract emulsification, cancer treatment, dental descaling, and ultrasonic scalpels are just a few of the advantageous industrial and therapeutic uses for low- frequency ultrasound. These characteristics make low-frequency sonophoresis especially useful for drug delivery, making it worthy of special attention in this context[40].Sonophoresis's precise process is unclear. Although cavitation is inversely related to frequency, it is believed to be effective for improving drug delivery. At the same time, high-intensity, low-frequency (<200 kHz) cavitation can increase the permeability of the skin more quickly in response to pressure changes caused by the movement of the sound wave[41]. By exhibiting a significant 26.2-fold improvement in drug transport, the creation of a conformable ultrasonic patch seeks to improve transdermal absorption of niacinamide. This novel device represents a major breakthrough in transdermal drug delivery technology and has the potential to be used in large-area, safe, and effective skin care and cosmetic therapeutic applications.[42]

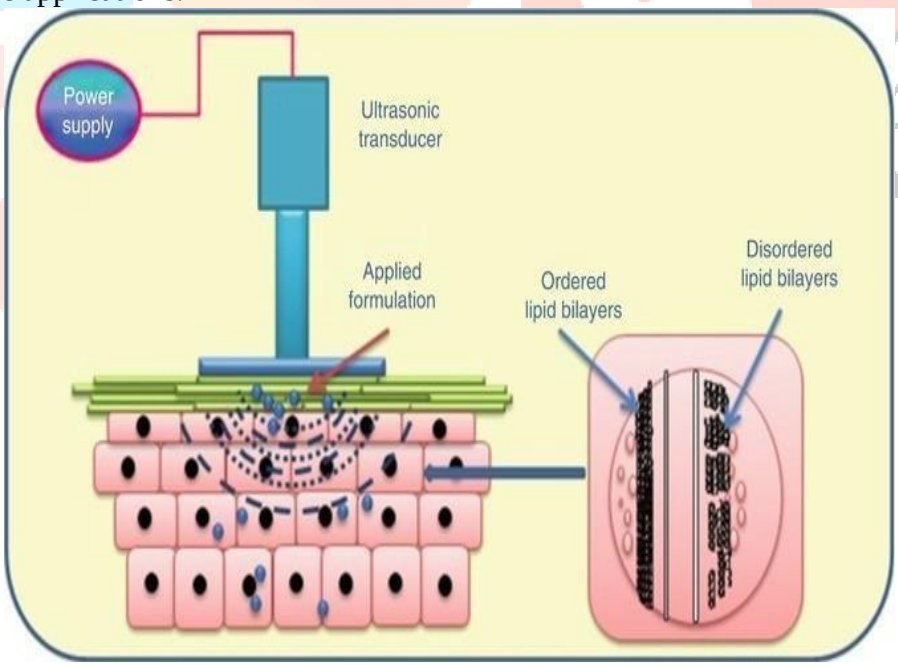

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Fig 3 sonophoreis

3) **Micro needle**

The first microneedles were discovered in 1976. Recently, ALZA Corp. unveiled a technology called Macro-flux, which has the unique benefit of working with different drug coatings and reservoirs. This cutting-edge transdermal drug administration method is becoming more and more well-liked for administering medications via needles. It includes a variety of needle varieties, each with its own mechanism of action, such as solid microneedles and microneedle patches. This technique is mostly used in the production of hydrogel and dissolving

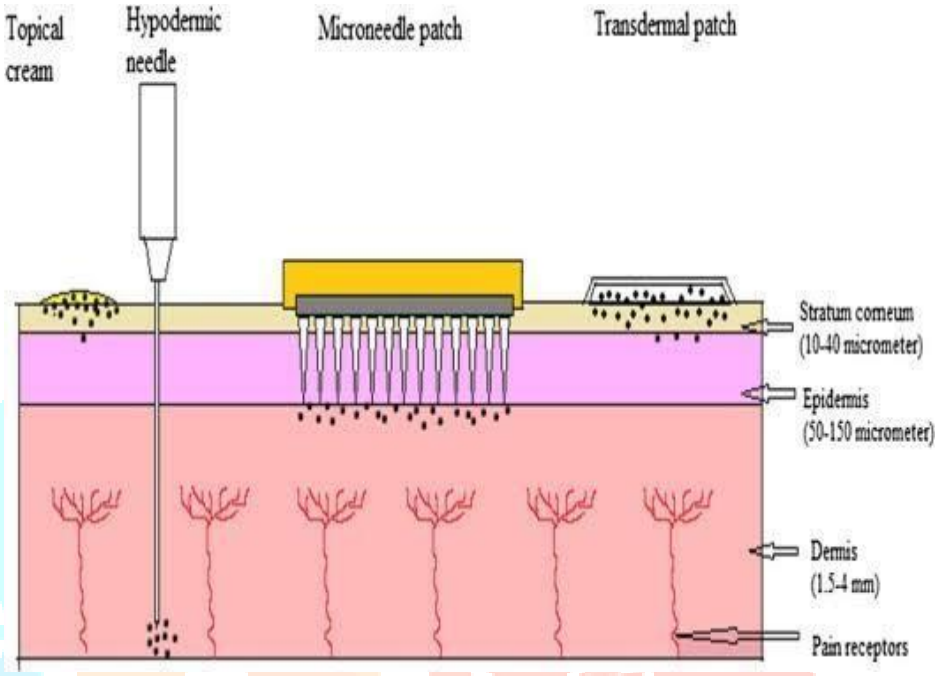

Fig 4 Microneedle mechanism

microneedles [43].The process of intricately creating microneedles, or photolithography, has the benefit of producing needles in a variety of shapes and materials. This technique is mostly used to create silicon or dissolving/hydrogel microneedles by etching photoresist to create an inverse mold based on the microneedle structure[44].Another safety concern with solid microneedles is that they can break inside the skin, posing a biohazard. The medication is transported into the skin using hollow microneedles' microfluidic channels from an external reservoir. They offer a way to store huge amounts of pharmaceuticals, but their production is difficult and requires cleanroom procedures. They also have the disadvantage of only being able to distribute drugs in liquid form[45].Despite the excellent mechanical strength of the produced polymer, the resulting microneedles' irregular geometry rendered them unsuitable for other uses. Porous microneedles made of polylactic acid (PLA) have been utilized to administer drugs transdermally, however they are weak and cannot penetrate the skin. [46]

4] TDDS using chemical enhancers Drugs must have specific qualities, such as a low molecular weight (less than 1 kDa), an affinity for both lipophilic and hydrophilic phases, a short half-life, and little potential to irritate skin, in order to improve transdermal delivery and therapeutic efficacy. Drug penetration is influenced by a number of factors. Through the skin, such as the species, age, location, temperature, and condition of the skin, as well as the application site, duration of exposure, moisture content, preparation techniques, and the drug's physicochemical characteristics. Aspects of transdermal medication delivery technology have been the main focus of recent study[47].One or more of the following three primary processes may be used by penetration enhancers: [48]

1. Disruption of the stratum corneum lipid's highly organized structure.
2. Interaction with proteins inside cells.
3. Better medication, coenhancer, or solvent distribution inside the stratum corneum. Transdermal permeation enhancers have been thoroughly researched to help chemicals move through the SC more easily. More than 360 substances, such as terpenes, sulphoxides, laurocapram, ,pyrrolidones, alcohol and glycol,

fatty acids and fatty alcohols, urea, surfactants, and so forth [49].Nevertheless, because of their few transdermal products that are now on the market have been regularly included due to formulation incompatibility or local irritation problems [50].

5) Iontophoresis

It has been demonstrated that iontophoresis increases the release rate of a number of medications with poor absorption/permeation profiles and improves skin penetration by encouraging the movement of ions across the membrane under the influence of a tiny externally applied potential difference (less than 0.5 mA/cm2). By applying an electrochemical potential gradient , this method has been used to transport ionic or nonionic medications in vivo.[51]The polarity, valency, and mobility of the therapeutic molecule, the type of applied electrical cycle, and the drug formulation all affect how effective iontophoresis is. Specifically, unlike the majority of other drug delivery technologies, iontophoresis relies on current, which reduces its reliance on biological parameters for drug absorption[52].In addition to iontophoresis, additional technologies have been employed to improve transdermal medication transport, including electroporation, chemical enhancers, and ultrasound. For TDDS, the combinational iontophoresis methods listed below have been employed Iontophoresis Plus Substances Iontophoresis in conjunction with ultrasound and electroporation[53]. The iontophoretic method can enhance the transdermal distribution of proteins and peptides with a reduce current intensity in a brief amount of time. Iontophoresis is a process that uses electrical current to "permeate ionized drug molecules across biological membranes," or it can be described as passage of a direct or periodic electric current through an electrolyte solution containing the ionic molecules to be delivered using the proper electrode polarity, resulting in the delivery of charged or ionic molecules into a tissue. [54]

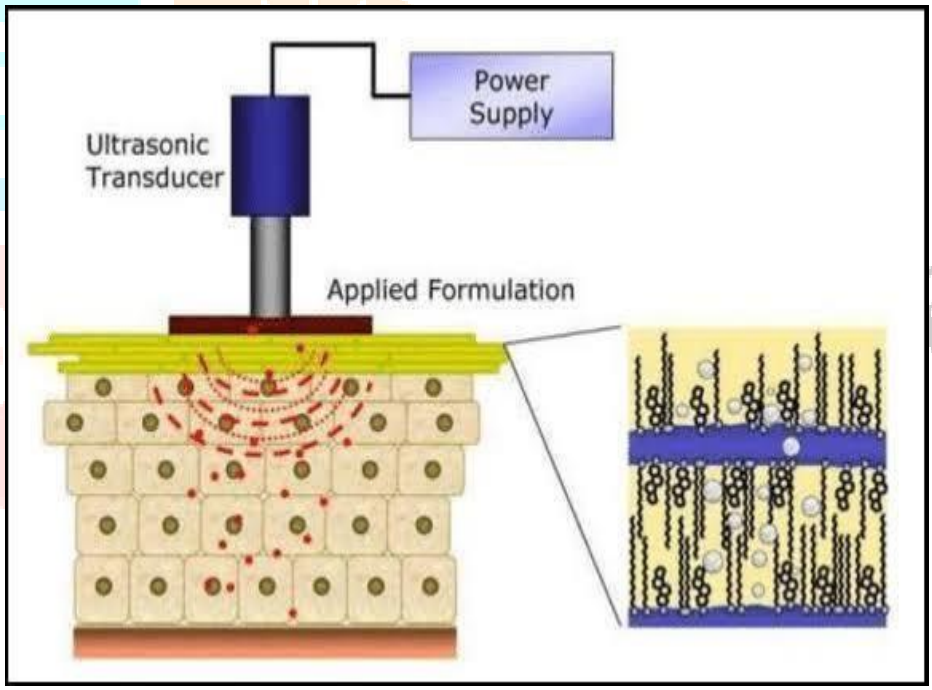

Fig 5 Iontophoresis

Applications

ANTI-AGING

The accumulation of damage brought on by a range of stresses causes aging, a pervasive biological process that leads to a cumulative and irreversible loss in physical function across all organ systems. Remarkably, studies conducted in 1925 found that light intensity may affect Drosophila development rate and lifespan[55]. The slow shrinking of homeodynamic space is the hallmark of aging[56,57].An intricate biological process, skin aging is impacted by both exogenous or extrinsic (chronic light exposure, pollution, ionizing radiation, chemicals, and toxins) and endogenous or intrinsic (genetics, cellular metabolisms, hormones, and metabolic processes) factors[58]. Over time, skin changes beautifully! Collagen levels decline, moisture levels fall, and cell renewal slows as we age naturally. However, skin remains resilient and glowing with proper maintenance. Desire to investigate Natural aging causes a loss in collagen, a decrease in hydration, and a slowdown remains resilient and glowing with proper care. Wish to learn more about lifestyle, science, or skincare[59,60,61].Premature photoaged skin usually exhibits a thicker epidermis, mottled discolouration, deep

wrinkles, laxity, dullness, and roughness in contrast to thin and atrophic, finely wrinkled, and dry naturally aged skin. [62,63,64,65,66,67]

SKIN BRIGHTENING

In many Asian cultures, lighter skin tones are frequently linked to brightness and even complexion. Consequently, the market for skin-brightening products keeps expanding, especially in nations like China, India, and Japan[68].Many modern skin-brightening products now focus on safe and effective ingredients that help achieve a radiant Complexion. For example, niacinamide is known for reducing dark spots and improving skin texture, while vitamin C brightens the skin and protects against environmental damage. Licorice extract and arbutin gently fade hyperpigmentation without irritation. These advancements provide individuals with options that promote an even skin tone while maintaining skin health and hydration[69,70].Medical professionals utilize skin-lightening solutions to treat a variety of skin conditions, including hyperpigmentation[71]. Nonetheless, a sizable market has emerged as a result of the rising need for cosmetics. Natural, semi-synthetic, or synthetic materials can be used as cosmetic ingredients, providing a variety of choices and affecting the halal status of goods. [72]

ACNE TREATMENT

The follicular sebaceous units are the main target of acne, a persistent inflammatory skin condition. Acne is most common in people between the ages of 15 and 20. Although it Declines during puberty, acne is very uncommon in preadolescent children. But it's important to remember that a sizable percentage of people still have acne [73].The skin is a very dynamic organ that serves as a barrier of defense between the body's internal systems and the outside world. It makes up one-sixth of the body weight. In addition to providing protection from microbiological and physical dangers, it also controls body temperature, keeps the body hydrated, permits sensory perception, and is essential for immune defense. [74]

Challenges and future prospects

Future Challenges and Opportunities of TDD is noninvasive and is regarded as relatively simple to use in younger and older patients, even in pediatric and geriatric patients. Their goal is to improve the administration of medications that typically encounter difficulties related to low penetration flux and effectiveness. Nevertheless, the creation of active patches that employ these technologies has encountered challenges regarding market success, technical difficulties, and consumer acceptance. These technologies' effectiveness in delivering medications is somewhat offset by their reliance on electrically powered, electronically controlled devices, which limits their use and raises their cost. Techniques that puncture tiny holes in the skin, like thermal poration, jet injection, and micro needles, can significantly boost transdermal delivery of tiny medications, macromolecules, and even particles however, more research is required to determine cost-effectiveness, safety, and skin damage.

CONCLUSION

The transdermal method of drug delivery is gaining popularity as a result of advancements in technology. Due to its enhanced therapeutic capabilities, transdermal drug delivery systems (TDDS) can develop effective medications that incorporate both hydrophilic and hydrophobic active substance. As a result transdermal drug delivery system (TDDS) is one of the fastest growing technologies in pharmaceutical industries.

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